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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

02076254.8

PRIORITY DOCUMENT
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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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R C van Dijk

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Radiolabelled quinoline and quinolinone derivatives and their use as metabotropic glutamate receptor ligands

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RADIOLABELLED QUINOLINE AND QUINOLINONE DERIVATIVES AND THEIR USE AS METABOTROPIC GLUTAMATE RECEPTOR LIGANDS.

The present invention is concerned with radiolabelled quinoline and quinolinone derivatives showing metabotropic glutamate receptor antagonistic activity, in particular mGlu1 receptor activity, and their preparation ; it further relates to compositions comprising them, as well as their use in a diagnostic method, in particular for marking and identifying metabotropic glutamate receptor sites and for imaging an organ.

Introduction

The neurotransmitter glutamate is considered to be the major excitatory neurotransmitter in the mammalian central nervous system. The binding of this neurotransmitter to metabotropic glutamate receptors (mGluRs), which are a subfamily of the G-protein-coupled receptors and which comprise 8 distinct subtypes of mGluRs, namely mGluR1 through mGluR8, activates a variety of intracellular second messenger systems. The mGluRs can be divided into 3 groups based on amino acid sequence homology, the second messenger system utilized by the receptors and the pharmacological characteristics. Group I mGluRs, which comprises mGluR subtype 1 and 5, couple to phospholipase C and their activation leads to intracellular calcium-ion mobilization. Group II mGluRs (mGluR2 and 3) and group III mGluRs (mGluR4, 6, 7 and 8) couple to adenyl cyclase and their activation causes a reduction in second messenger cAMP and as such a dampening of the neuronal activity. Treatment with Group I mGluR antagonists has been shown to translate in the parasynapsis into a reduced release of neurotransmitter glutamate and to decrease the glutamate-mediated neuronal excitation via postsynaptic mechanisms. Since a variety of pathophysiologic processes and disease states affecting the central nervous system are thought to be due to excessive glutamate induced excitation of the central nervous system neurons, Group I mGluR antagonists, in particular mGluR1 antagonists could be therapeutically beneficial in the treatment of central nervous system diseases, in particular in psychiatric and neurological diseases.

However, up to now, no specific mGluR1-ligands were available, a lack severely hampering the study of the mGlu1 receptors, in particular the radioautographic investigations of the unequivocal distribution and abundance of these receptors in brain sections.. For group I, only [^{3}H]glutamate was available so far, being used on rat (Thomsen et al., <u>Brain Res.</u> 619, 22-28, 1993) or human (Kingston et al., 1998) mGlu1a

receptors. For the mGlu1a receptor and the mGlu5 receptor [^{3}H]quisqualate is available, however, said receptor is not specific for the mGlu1 receptor (it also binds to the AMPA receptor) and it is competitive, i.e. it displaces glutamate (Mutel at al., J. Neurochem., 75, 2590-2601, 2000).

It has been the goal of this invention to provide suitable specific, in particular non-competitive mGlu1-receptor ligands.

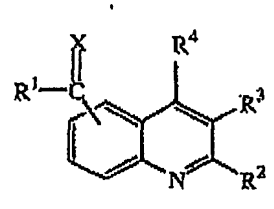
The inventors have now found a particular group of compounds that - in a radiolabelled form - provides for suitable specific, in particular non-competitive mGlu1 receptor ligands as well as a method for marking and identifying metabotropic glutamate receptor sites and for imaging an organ.

In the framework of this application, the term "specific" means that the ligand binds preferentially to the mGlu1 receptor site. The term "non-competitive" means that the ligand does not or only marginally displaces glutamate bonded to the mGlu1 receptor site.

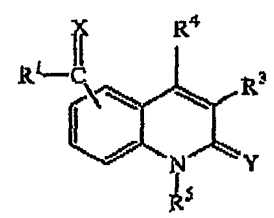
WO 99/26927 discloses antagonists of Group I mGluRs for treating neurological diseases and disorders, based – among others – on a quinoline structure.
WO 99/03822 discloses bicyclic metabotropic glutamate receptor ligands, none of them based on a quinoline or quinolinone structure.

Detailed Description

The present invention concerns the radiolabelled compounds of Formula (I-A)* or (I-B)*



(I-A)*

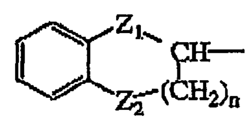


(I-B)*

an *N*-oxide form, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemical isomeric form thereof, wherein

X represents O; $C(R^6)_2$ with R^6 being hydrogen, aryl or C_{1-6}alkyl optionally substituted with amino or mono- or di(C_{1-6}alkyl)amino; S or N-R^7 with R^7 being amino or hydroxy;

R^1 represents C_{1-6}alkyl; aryl; thienyl; quinolinyl; cycloC_{3-12}alkyl or (cycloC_{3-12}alkyl)C_{1-6}alkyl, wherein the cycloC_{3-12}alkyl moiety optionally may contain a double bond and wherein one carbon atom in the cycloC_{3-12}alkyl moiety may be replaced by an oxygen atom or an NR^8-moiety with R^8 being hydrogen, benzyl or C_{1-6}alkyloxycarbonyl ; wherein one or more hydrogen atoms in a C_{1-6}alkyl-moiety or in a cycloC_{3-12}alkyl-moiety optionally may be replaced by C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, aminoC_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, halo, C_{1-6}alkyloxycarbonyl, aryl, amino, mono– or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, halo, piperazinyl, pyridinyl, morpholinyl, thienyl or a bivalent radical of formula –O–, -O-CH_2-O or –O-CH_2-CH_2-O-; or a radical of formula (a-1)

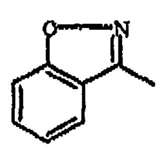


a-1

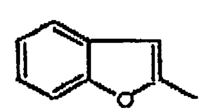
wherein Z_1 is a single covalent bond, O, NH or CH_2;
Z_2 is a single covalent bond, O, NH or CH_2;
n is an integer of 0, 1, 2 or 3;
and wherein each hydrogen atom in the phenyl ring independently may optionally be replaced by halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy or hydroxyC_{1-6}alkyl;

or X and R^1 may be taken together with the carbon atom to which X and R^1 are attached to form a radical of formula (b-1), (b-2) or (b-3);

b-1



b-2



b-3

R^2 represents hydrogen; halo; cyano; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkylthio; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylcarbonyloxyC_{1-6}alkyl;

C_{2-6}alkenyl; hydroxyC_{2-6}alkenyl; C_{2-6}alkynyl; hydroxyC_{2-6}alkynyl; tri(C_{1-6}alkyl)silaneC_{2-6}alkynyl; amino; mono– or di(C_{1-6}alkyl)amino; mono– or di(C_{1-6}alkyloxyC_{1-6}alkyl)amino; mono– or di(C_{1-6}alkylthioC_{1-6}alkyl)amino; aryl; arylC_{1-6}alkyl; arylC_{2-6}alkynyl; C_{1-6}alkyloxyC_{1-6}alkylaminoC_{1-6}alkyl; aminocarbonyl optionally substituted with C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl or pyridinylC_{1-6}alkyl;

a heterocycle selected from thienyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, piperidinyl and piperazinyl, optionally N-substituted with C_{1-6}alkyloxyC_{1-6}alkyl, morpholinyl, thiomorpholinyl, dioxanyl or dithianyl ;

a radical –NH-C(=O)R^9 wherein R^9 represents

C_{1-6}alkyl optionally substituted with cycloC_{3-12}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aryl, aryloxy, thienyl, pyridinyl, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylthio, benzylthio, pyridinylthio or pyrimidinylthio;

cycloC_{3-12}alkyl; cyclohexenyl; amino; arylcycloC_{3-12}alkylamino; mono-or-di(C_{1-6}alkyl)amino; mono- or di(C_{1-6}alkyloxycarbonylC_{1-6}alkyl)amino; mono- or di(C_{1-6}alkyloxycarbonyl)amino; mono-or di(C_{2-6}alkenyl)amino; mono- or di(arylC_{1-6}alkyl)amino; mono- or diarylamino; arylC_{2-6}alkenyl; furanylC_{2-6}alkenyl; piperididinyl; piperazinyl; indolyl; furyl; benzofuryl; tetrahydrofuryl; indenyl; adamantyl; pyridinyl; pyrazinyl; aryl; arylC_{1-6}alkylthio or a radical of formula (a-1) ;

a sulfonamid -NH-SO_2-R^{10} wherein R^{10} represents C_{1-6}alkyl, mono- or poly haloC_{1-6}alkyl, arylC_{1-6}alkyl, arylC_{2-6}alkenyl, aryl, quinolinyl, isoxazolyl or di(C_{1-6}alkyl)amino;

R^3 and R^4 each independently represent hydrogen; halo; hydroxy; cyano; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyloxyC_{1-6}alkyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{2-6}alkenyl; hydroxyC_{2-6}alkenyl; C_{2-6}alkynyl; hydroxyC_{2-6}alkynyl; tri(C_{1-6}alkyl)silaneC_{2-6}alkynyl; amino; mono– or di(C_{1-6}alkyl)amino; mono– or di(C_{1-6}alkyloxyC_{1-6}alkyl)amino; mono– or di(C_{1-6}alkylthioC_{1-6}alkyl)amino; aryl; morpholinylC_{1-6}alkyl or piperidinylC_{1-6}alkyl ; or

R^2 and R^3 may be taken together to form –R^2-R^3–, which represents a bivalent radical of formula –$(CH_2)_3$–, –$(CH_2)_4$–, –$(CH_2)_5$–, –$(CH_2)_6$–, –CH=CH-CH=CH-, -Z_4-CH=CH-, -CH=CH-Z_4-, –Z_4-CH_2-CH_2-CH_2-, -CH_2-Z_4-CH_2-CH_2-, -CH_2-CH_2-Z_4-CH_2-,

-CH_2-CH_2-CH_2-Z_4-, -Z_4-CH_2-CH_2-, -CH_2-Z_4-CH_2- or -CH_2-CH_2-Z_4-, with Z_4 being

O, S, SO_2 or NR^{11} wherein R^{11} is hydrogen, C_{1-6}alkyl, benzyl or C_{1-6}alkyloxycarbonyl; and wherein each bivalent radical is optionally substituted with C_{1-6}alkyl.

or R^3 and R^4 may be taken together to form a bivalent radical of formula -CH=CH-CH=CH- or $-CH_2-CH_2-CH_2-CH_2-$;

R^5 represents hydrogen; cycloC_{3-12}alkyl; piperidinyl; oxo-thienyl; tetrahydrothienyl, arylC_{1-6}alkyl; C_{1-6}alkyloxyC_{1-6}alkyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl or C_{1-6}alkyl optionally substituted with a radical $C(=O)NR_xR_y$, in which R_x and R_y, each independently are hydrogen, cycloC_{3-12}alkyl, C_{2-6}alkynyl or C_{1-6}alkyl optionally substituted with cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, furanyl, pyrrolidinyl, benzylthio, pyridinyl, pyrrolyl or thienyl;

Y represents O or S;

or Y and R^5 may be taken together to form $=Y-R^5-$ which represents a radical of formula

-CH=N-N=	(c-1);
-N=N-N=	(c-2); or
-N-CH=CH-	(c-3);

aryl represents phenyl or naphthyl optionally substituted with one or more substituents selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, phenyloxy, nitro, amino, thio, C_{1-6}alkylthio, haloC_{1-6}alkyl, polyhaloC_{1-6}alkyl, polyhaloC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino; mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyano, $-CO-R^{12}$, $-CO-OR^{13}$, $-NR^{13}SO_2R^{12}$, $-SO_2-NR^{13}R^{14}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{13}R^{14}$, $-SOR^{12}$, $-SO_2R^{12}$; wherein each R^{12}, R^{13} and R^{14} independently represent C_{1-6}alkyl; cycloC_{3-6}alkyl; phenyl; phenyl substituted with halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, haloC_{1-6}alkyl, polyhaloC_{1-6}alkyl, furanyl, thienyl, pyrrolyl, imidazolyl, thiazolyl or oxazolyl;

and when the $R^1-C(=X)$ moiety is linked to another position than the 7 or 8 position, then said 7 and 8 position may be substituted with R^{15} and R^{16} wherein either one or both of R^{15} and R^{16} represents C_{1-6}alkyl, C_{1-6}alkyloxy or R^{15} and R^{16} taken together may form a bivalent radical of formula -CH=CH-CH=CH-.

As used in the foregoing definitions and hereinafter C_{1-6}alkyl as a group or part of a group encompasses the straight and branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, pentyl or hexyl; C_{2-6}alkenyl as a group or part of a group encompasses the straight and branched chain hydrocarbon radicals having from 2 to 6 carbon atoms and having a

double bond such as ethenyl, propenyl, butenyl, pentenyl, hexenyl, 3-methylbutenyl and the like; C_{2-6}alkynyl as a group or part of a group defines straight or branched chain hydrocarbon radicals having from 2 to 6 carbon atoms and having a triple bond such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, 3-methylbutynyl and the like; cycloC_{3-6}alkyl encompasses monocyclic alkyl ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl; cycloC_{3-12}alkyl encompasses mono-, bi- or tricyclic alkyl ring structures and is generic to for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornanyl, adamantyl.

The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhaloC_{1-6}alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C_{1-6}alkyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl. In case more than one halogen atoms are attached to an alkyl group within the definition of polyhaloC_{1-6}alkyl, they may be the same or different.

When any variable, e.g. aryl, occurs more than one time in any constituent, each definition is independent.

When any bond is drawn into a ring structure, it means that the corresponding substituent may be linked to any atom of said ring structure. This means for instance that the R^1-C(=X) moiety may be linked to the quinoline or quinolinone moiety in position 5, 6, 7, 8 but also position 3 or position 4.

By the term "radiolabelled compound" is meant any compound according to Formula (I-A)* or (I-B)*, an *N*-oxide form, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, which contains at least one radioactive atom. In the framework of this application, compounds which do not contain a radio-active atom are denoted without an asterisk to their formula number, compounds which contain a radio-active atom are denoted with an asterisk to their formula number.

In particular, the radioactive atom is selected from the group of hydrogen, carbon, nitrogen, sulfur, oxygen and halogen. Preferably, the radioactive atom is selected from the group of hydrogen, carbon and halogen.

In particular, the radioactive atom is selected from the group of ^{3}H, ^{11}C, ^{18}F, ^{122}I, ^{123}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br. Preferably, the radioactive atom is selected from the group of ^{3}H, ^{11}C and ^{18}F.

By the term "compound according to the invention" is meant a compound according to Formula (I-A)* or (I-B)*, an *N*-oxide form, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof.

For *in vivo* use, salts of the compounds of Formula (I-A)* and (I-B)* are those wherein the counter ion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention. With the term "in vivo" is meant any use of the compounds according to the invention whereby said compounds are administered to live animals.

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of Formula (I-A)* and (I-B)* are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

The compounds of Formula (I-A)* and (I-B)* containing acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. primary, secondary and tertiary aliphatic and aromatic amines such as methylamine, ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine, diethylamine, diethanolamine, dipropylamine,

diisopropylamine, di-n-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline, the benzathine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term "addition salt" also comprises the hydrates and solvent addition forms which the compounds of Formula (I-A)* and (I-B)* are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term "quaternary amine" as used hereinbefore defines the quaternary ammonium salts which the compounds of Formula (I-A)* and (I-B)* are able to form by reaction between a basic nitrogen of a compound of Formula (I-A)* or (I-B)* and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, e.g. methyliodide or benzyliodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl p-toluenesulfonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counter ions include chloro, bromo, iodo, trifluoroacetate and acetate. The counter ion of choice can be introduced using ion exchange resins.

It will be appreciated that some of the compounds according to the invention may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms which the compounds according to the invention or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereoisomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure as well as each of the individual isomeric forms of the compounds according to the invention, substantially free, i.e. associated with less than 10 %, preferably less than 5 %, in particular less than 2% and most preferably less than 1 % of the other isomers. Stereochemically isomeric forms of the compounds according to the invention are obviously intended to be embraced within the scope of the present invention. The same applies to the intermediates as described herein, used to prepare end products of the compounds according to the invention.

The terms *cis* and *trans* are used herein in accordance with Chemical Abstracts nomenclature.

In some compounds according to the invention and in the intermediates used in their preparation, the absolute stereochemical configuration has not been determined. In these cases, the stereoisomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. However, said "A" and "B" stereoisomeric forms can be unambiguously characterized by physicochemical characteristics such as their optical rotation in case "A" and "B" have an enantiomeric relationship. A person skilled in the art is able to determine the absolute configuration of such compounds using art-known methods such as, for example, X-ray diffraction. In case "A" and "B" are stereoisomeric mixtures, they can be further separated whereby the respective first fractions isolated are designated "A1" and "B1"and the second as "A2" and "B2", without further reference to the actual stereochemical configuration.

The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I-A)* and (I-B)* wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

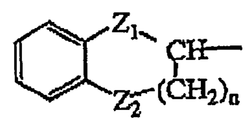
Some of the compounds according to the invention may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. Of special interest are those compounds of formula (I-A)* and (I-B)* which are stereochemically pure.

An interesting group of compounds are those compounds of formula (I-A)* and (I-B)* wherein

X represents O; $C(R^6)_2$ with R^6 being hydrogen or aryl ; or $N\text{-}R^7$ with R^7 being amino or hydroxy;

R^1 represents C_{1-6}alkyl, aryl; thienyl; quinolinyl; cycloC_{3-12}alkyl or (cycloC_{3-12}alkyl)C_{1-6}alkyl, wherein the cycloC_{3-12}alkyl moiety optionally may contain a double bond and wherein one carbon atom in the cycloC_{3-12}alkyl moiety may be replaced by an oxygen atom or an NR^8-moiety with R^8 being benzyl or C_{1-6}alkyloxycarbonyl ; wherein one or more hydrogen atoms in a C_{1-6}alkyl-moiety or in a cycloC_{3-12}alkyl-moiety optionally may be replaced by C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, halo, aryl, mono– or

di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, halo, piperazinyl, pyridinyl, morpholinyl, thienyl or a bivalent radical of formula –O- or -O-CH_2-CH_2-O-; or a radical of formula (a-1)

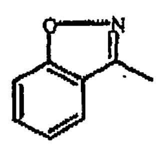


a-1

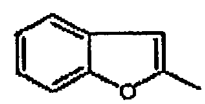
wherein Z_1 is a single covalent bond, O or CH_2;
Z_2 is a single covalent bond, O or CH_2;
n is an integer of 0, 1, or 2 ;
and wherein each hydrogen atom in the phenyl ring independently may optionally be replaced by halo or hydroxy;

or X and R^1 may be taken together with the carbon atom to which X and R^1 are attached to form a radical of formula (b-1), (b-2) or (b-3);

b-1



b-2



b-3

R^2 represents hydrogen; halo; cyano; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkylthio; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{2-6}alkenyl; hydroxyC_{2-6}alkenyl; C_{2-6}alkynyl; hydroxyC_{2-6}alkynyl; tri(C_{1-6}alkyl)silaneC_{2-6}alkynyl; amino; mono– or di(C_{1-6}alkyl)amino; mono– or di(C_{1-6}alkyloxyC_{1-6}alkyl)amino; mono– or di(C_{1-6}alkylthioC_{1-6}alkyl)amino; aryl; arylC_{1-6}alkyl; arylC_{2-6}alkynyl; C_{1-6}alkyloxyC_{1-6}alkylaminoC_{1-6}alkyl;
aminocarbonyl optionally substituted with C_{1-6}alkyloxycarbonylC_{1-6}alkyl ;
a heterocycle selected from thienyl, furanyl, thiazolyl and piperidinyl, optionally N-substituted with morpholinyl or thiomorpholinyl;
a radical –NH-C(=O)R^9 wherein R^9 represents C_{1-6}alkyl optionally substituted with cycloC_{3-12}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aryl, aryloxy, thienyl, pyridinyl, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylthio, benzylthio, pyridinylthio or pyrimidinylthio; cycloC_{3-12}alkyl; cyclohexenyl; amino; arylcycloC_{3-12}alkylamino; mono-or-di(C_{1-6}alkyl)amino; mono- or di(C_{1-6}alkyloxycarbonylC_{1-6}alkyl)amino; mono- or di(C_{1-6}alkyloxycarbonyl)amino; mono-or di(C_{2-6}alkenyl)amino; mono- or

di(arylC_{1-6}alkyl)amino; mono- or diarylamino; arylC_{2-6}alkenyl; furanylC_{2-6}alkenyl; piperididinyl; piperazinyl; indolyl; furyl; benzofuryl; tetrahydrofuryl; indenyl; adamantyl; pyridinyl; pyrazinyl; aryl or a radical of formula (a-1) ;
a sulfonamid -NH-SO_2-R^{10} wherein R^{10} represents C_{1-6}alkyl, mono- or poly haloC_{1-6}alkyl, arylC_{1-6}alkyl or aryl;

R^3 and R^4 each independently represent hydrogen; C_{1-6}alkyl; C_{1-6}alkyloxyC_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; or

R^2 and R^3 may be taken together to form $-R^2$-R^3-, which represents a bivalent radical of formula $-(CH_2)_4$-, $-(CH_2)_5$-, $-Z_4$-CH=CH-, $-Z_4$-CH_2-CH_2-CH_2- or -Z_4-CH_2-CH_2-, with Z_4 being O, S, SO_2 or NR^{11} wherein R^{11} is hydrogen, C_{1-6}alkyl, benzyl or C_{1-6}alkyloxycarbonyl; and wherein each bivalent radical is optionally substituted with C_{1-6}alkyl;

or R^3 and R^4 may be taken together to form a bivalent radical of formula -CH=CH-CH=CH- or $-CH_2$-CH_2-CH_2-CH_2- ;

R^5 represents hydrogen; piperidinyl; oxo-thienyl; tetrahydrothienyl, arylC_{1-6}alkyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl or C_{1-6}alkyl optionally substituted with a radical $C(=O)NR_xR_y$, in which R_x and R_y, each independently are hydrogen, cycloC_{3-12}alkyl, C_{2-6}alkynyl or C_{1-6}alkyl optionally substituted with cyano, C_{1-6}alkyloxy or C_{1-6}alkyloxycarbonyl;

Y represents O or S;

or Y and R^5 may be taken together to form =Y-R^5- which represents a radical of formula

-CH=N-N= (c-1); or
-N=N-N= (c-2);

aryl represents phenyl or naphthyl optionally substituted with one or more substituents selected from halo, C_{1-6}alkyloxy, phenyloxy, mono-or di(C_{1-6}alkyl)amino and cyano;

and when the R^1-C(=X) moiety is linked to another position than the 7 or 8 position, then said 7 and 8 position may be substituted with R^{15} and R^{16} wherein either one or both of R^{15} and R^{16} represents C_{1-6}alkyl or R^{15} and R^{16} taken together may form a bivalent radical of formula -CH=CH-CH=CH-.

A further most interesting group of compounds comprises those compounds of formula (I-A)* and (I-B)* wherein X represents O;

R^1 represents C_{1-6}alkyl; cycloC_{3-12}alkyl or (cycloC_{3-12}alkyl)C_{1-6}alkyl, wherein one or more hydrogen atoms in a C_{1-6}alkyl-moiety or in a cycloC_{3-12}alkyl-moiety optionally may be replaced by C_{1-6}alkyloxy, aryl, halo or thienyl;

R^2 represents hydrogen; halo; C_{1-6}alkyl or amino;

R^3 and R^4 each independently represent hydrogen or C_{1-6}alkyl; or

R^2 and R^3 may be taken together to form $-R^2-R^3-$, which represents a bivalent radical of formula $-Z_4-CH_2-CH_2-CH_2-$ or $-Z_4-CH_2-CH_2-$ with Z_4 being O or NR^{11} wherein R^{11} is C_{1-6}alkyl; and wherein each bivalent radical is optionally substituted with C_{1-6}alkyl;

or R^3 and R^4 may be taken together to form a bivalent radical of formula $-CH_2-CH_2-CH_2-CH_2-$;

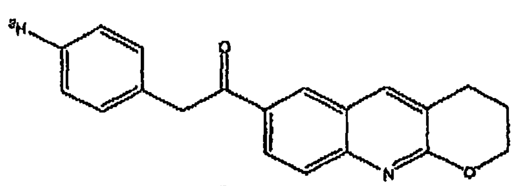
R^5 represents hydrogen;

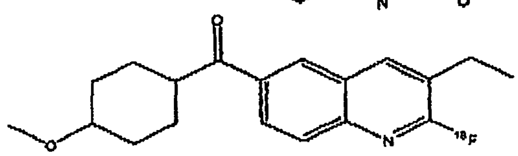
Y represents O; and

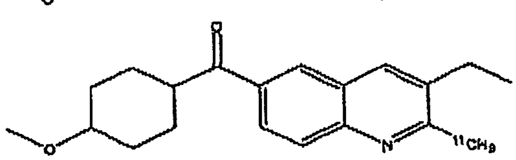
aryl represents phenyl optionally substituted with halo.

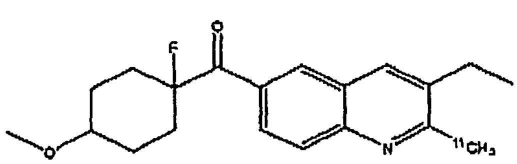
A further interesting group of compounds comprises those compounds of formula (I-A)* and (I-B)* wherein the R^1-C(=X) moiety is linked to the quinoline or quinolinone moiety in position 6.

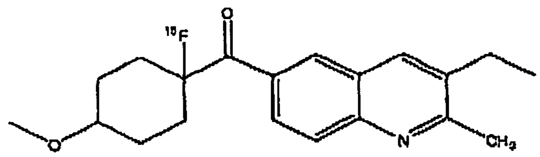
Especially interesting are the following radioactive compounds :











All compounds according to the invention show a moderate to strong mGluR1 activity. Such activity is among others attributed to the specific binding of said compound to the mGlu1 receptor, which makes the compounds useful in a diagnostic method, e.g. for labeling and detecting mGlu1 receptor sites. The invention therefore also relates to a radiolabelled compound according to the invention for use in a diagnostic method.

<u>First preferred embodiment</u>

According to a first preferred embodiment, the radiolabelled compound comprises at least one [^{3}H]-atom or one [^{125} I]-atom. A [^{3}H]-atom is conveniently introduced by partially or completely substituting one or more non-radioactive [^{1}H]-hydrogen atoms in the molecule by their radioactive isotopes. The choice of whether a [^{3}H] or [^{125}I] radioligand will be used may depend in part on the availability of liquid scintillation counters (LSC), which are fairly expensive. [^{125} I] ligands can be quantified using either a γ-counter or an LSC, whereas [^{3}H] ligands necessitate the use of an LSC.

The radiolabelled compound comprising at least one [^{3}H]-atom or one [^{125} I]-atom is advantageously used in radioligand-binding techniques, in particular in *in vitro* membrane receptor assays for marking or identifying a mGlu1 receptor in biological material.

The radiolabelled compounds comprising at least one [^{3}H]-atom or one [^{125} I]-atom is also advantageously used in *in vivo* mGlu1 receptor autoradiography of the brain since the compounds according to the invention have the advantageous and unexpected ability to readily cross the blood-brain barrier.

The invention therefore also relates to a radiolabelled compound according to the invention used in a diagnostic method which consists of marking or identifying a mGlu1 receptor in biological material, as well as the use of the compounds according to the invention for the manufacture of a diagnostic tool for marking or identifying an mGlu1 receptor in biological material, whether *in vivo* or *in vitro*.

In the framework of this application, by the term "biological material" is meant to include any material which has a biological origin. In particular, this relates to tissue samples, plasma fluids, body fluids, body parts and organs originating from warm-blooded animals and warm-blooded animals *per se*, in particular humans.

Basic experiments that are performed using the membrane assay system for marking or identifying a mGlu1 receptor in biological material are : saturation experiments, inhibition experiments, association kinetic experiments and dissociation kinetic experiments. These methods are applicable to most neurotransmitter and hormone receptor systems, including the mGluR1-system (Methods for Neurotransmitter Receptor Analysis, ed. by Henry I. Yamamura et al., Raven Press Ltd., New York, 1990). To this end, the radiolabelled compound is administered to the biological material to mark the mGlu1 receptors and the emissions from the radiolabelled compound are detected to identify the amount or location of the mGlu1 receptors, for instance for *ex vivo* receptor autoradiography.

The radiolabelled compounds according to the invention comprising at least one [^{3}H]-atom or one [^{125} I]-atom are also useful as agents for screening whether a test compound has the ability to occupy or bind to a mGlu1 receptor site. The degree to which a test compound will displace a compound according to the invention from the mGlu1 receptor site will show the test compound ability to occupy or bind to a mGluR1 receptor and therefore act as either an agonist, an antagonist or a mixed agonist/antagonist of a mGlu1 receptor.

The radiolabelled compounds according to the invention comprising at least one [^{3}H]-atom or one [^{125} I]-atom are advantageously prepared by substituting a halogen atom with a tritium atom, as is documented in the Experimental Section below.

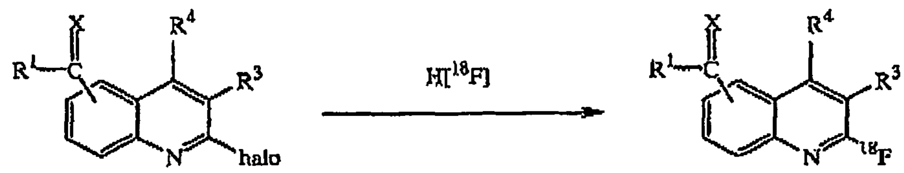
Second Preferred Embodiment

In a second preferred embodiment, the radiolabelled compound comprises at least one radioactive carbon or halogen atom. In principle, any compound according to Formula (I) containing a carbon or halogen atom is prone for radiolabel ling by replacing the carbon or halogen atom by a suitable radioactive isotope or by making the compounds according to Formula (I) using radioactively-labelled reagentia. Suitable halogen radioisotopes to this purpose are radioactive carbon, e.g. [^{11}C] ; radioactive iodides, e.g. [^{122}I], [^{123}I], [^{131}I] ; radioactive bromides, e.g. [^{75}Br], [^{76}Br], [^{77}Br] and [^{82}Br] ; and radioactive fluorides, e.g. [^{18}F]. Preferred radiolabelled compounds are those

compounds of Formula (I-A)* and (I-B)*, wherein R^1 is a radioactive carbon or halo atom, especially [^{11}C], [^{18}F], [^{123}I], [^{75}Br], [^{76}Br] or [^{77}Br].

Preparation of the radioactive compounds

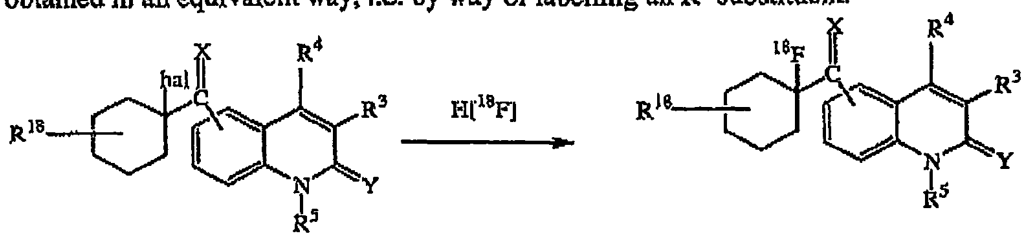
The introduction of a radioactive halogen atom can be performed by a suitable reaction such as depicted below



(I-A-a) (I-A-a)*

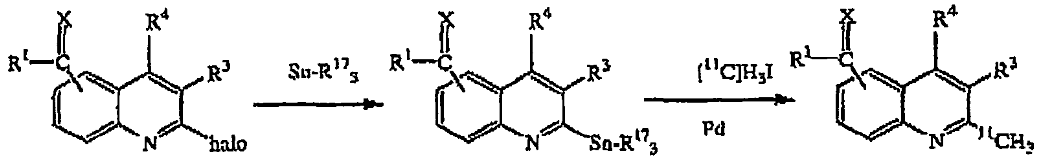
in which all substituents in Formula (I-A-a) and (I-A-a)* are defined as in Formula (I-A)* and halo is a halogen atom. A suitable compound (I-A-a) is reacted with H[^{18}F] such that the halogen atom present on the quinoline ring is displaced by a nucleophilic displacement reaction with the radioactive [^{18}F] atom.

For obtaining radiolabelled compounds according to Formula (I-B)*, radiolabel ling can be performed on an equivalent way, for instance by way of a reaction scheme as depicted below. Obviously, also compounds according to Formula (I-A)* can be obtained in an equivalent way, i.e. by way of labelling an R^1 substituent.



(I-B-a) (I-B-a)*

The introduction of a radioactive [^{11}C] can be performed using the reaction scheme below in which a suitable compound (I-A-a) is first stanyllated after which the radioactive [^{11}C] is introduced using e.g. a palladium catalyzed "Stille-type" coupling reaction using [^{11}C]methyliodide (Scott, W.J.; Crisp, G.T.; Stille, J.K. *J. Am. Chem. Soc., 1984, 106*, 4630).



(I-A-a) (I-A-b) (I-A-c)*

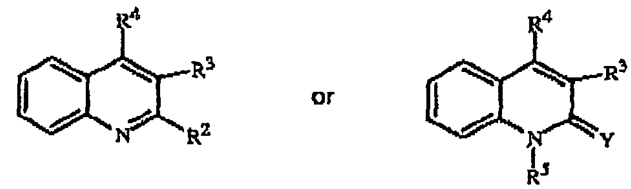
In Formula (I-A-a), (I-A-b) and (I-A-c)*, all substituents have the same meaning as defined in Formula (I-A)*, halo is a halogen atom and R^{17} is methyl or butyl.

Because of their unexpected property to penetrate readily the blood-brain barrier, the radiolabelled compounds comprising a radioactive halogen atom are advantageously administered *in vivo*, in an appropriate composition to an animal, especially a warm-blooded animal, and the location of said radiolabelled compounds is detected using imaging techniques, such as, for instance, Single Photon Emission Computered Tomography (SPECT) or Positron Emission Tomography (PET) and the like. In this manner the distribution of mGlu1 receptor sites throughout the body can be detected and organs containing mGlu1 receptor sites such as, for example, the brain, can be visualized by the imaging techniques mentioned hereinabove. This process of imaging an organ by administering a radiolabelled compound of Formula (I-A)* or (I-A)*, which bind to the mGlu1 receptor sites and detecting the emissions from the radioactive compound also constitutes an aspect of the present invention.

The application of the compounds of Formula (I-A)* and (I-B)* in the above described techniques constitutes a further aspect of the present invention. The invention in particular relates to the use of the compounds according to the invention for the manufacture of a diagnostic tool for use in PET. For use in PET, most preferred are radiolabelled compounds according to the invention, in which a ^{18}F is incorporated (US 4,931,270 by Horn et al., publiced June 5, 1990).

<u>Preparation of the non-radioactive compounds</u>
The non-radioactive compounds according to the invention may be produced in a number of ways.

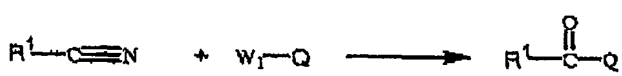
In order to simplify the structural representation of some of the present compounds and intermediates in the following preparation procedures, the quinoline or the quinolinone moiety will hereinafter be represented by the symbol Q.

Q = 

The compounds of formula (I-A) or (I-B), wherein X represents O, said compounds being represented by formula ($I_{A/B}$-a), can be prepared by oxidizing an intermediate of formula (II) in the presence of a suitable oxidizing agent, such as potassium permanganate, and a suitable phase-transfer catalyst, such as tris(dioxa-3,6-heptyl)amine, in a suitable reaction-inert solvent, such as for example dichloromethane.

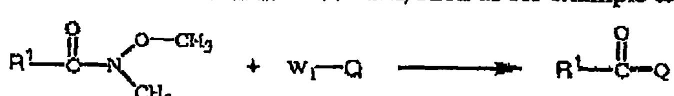
(II) ($I_{A/B}$-a)

Compounds of formula ($I_{A/B}$-a) may also be prepared by reacting an intermediate of formula (III) with an intermediate of formula (IV), wherein W_1 represents a halo atom, e.g. bromo, in the presence of butyl lithium and a suitable reaction-inert solvent, such as for example tetrahydrofuran.



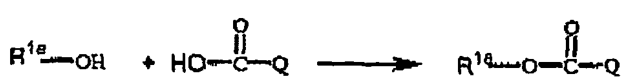
(III) (IV) ($I_{A/B}$-a)

Alternatively, compounds of formula ($I_{A/B}$-a) may also be prepared by reacting an intermediate of formula (V) with an intermediate of formula (IV) in the presence of butyl lithium and a suitable reaction-inert solvent, such as for example tetrahydrofuran.



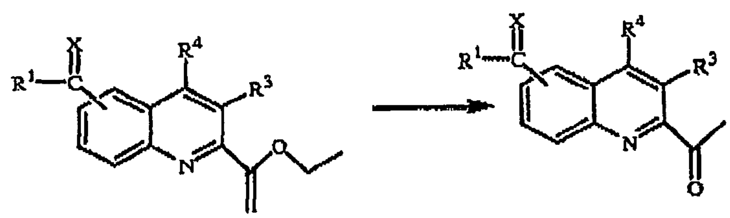
(V) (IV) ($I_{A/B}$-a)

Compounds of formula ($I_{A/B}$-a), wherein the R^1 substituent is linked to the carbonyl moiety via an oxygen atom, said R^1 substituent being represented by O-R^{1a} and said compounds by formula ($I_{A/B}$-a-1), can be prepared by reacting an intermediate of formula (VI) with an intermediate of formula (VII) in the presence of a suitable acid, such as sulfuric acid.



(VI) (VII) ($I_{A/B}$-a-1)

Compounds of formula (I-A), wherein R^2 represents methylcarbonyl, said compounds being represented by formula (I-A-1), can be prepared by reacting an intermediate of formula (VIII) in the presence of a suitable acid, such as hydrochloric acid, and a suitable reaction-inert solvent, such as for example tetrahydrofuran.



(VIII) (I-A-1)

The compounds of formula (I) may also be converted into each other following art-known transformations.

Compounds of formula (I-A) wherein R^2 is a halo atom, such as chloro, can be converted into a compound of formula (I-A), wherein R^2 is another halo atom, such as fluoro or iodo, by reaction with a suitable halogenating agent, such as for example potassium fluoride or sodium iodide, in the presence of a suitable reaction-inert solvent, e.g. dimethyl sulfoxide or acetonitrile and optionally in the presence of acetyl chloride.

Compounds of formula (I-A), wherein R^2 is a suitable leaving group, such as a halo atom, e.g. chloro, iodo, said leaving group being represented by W^2 and said compounds by (I-A-2), can be converted into a compound of formula (I-A) wherein R^2 is cyano, said compound being represented by formula (I-A-3), by reaction with a suitable cyano-introducing agent, such as for example trimethylsilanecarbonitrile, in the presence of a suitable base such as *N,N*-diethylethanamine and a suitable catalyst, such as for example tetrakis(triphenylphosphine)palladium.

Compounds of formula (I-A-2) can also be converted into a compound of formula (I-A-4) by reaction with C_{2-6}alkynyltri(C_{1-6}alkyl)silane in the presence of CuI, an appropriate base, such as for example *N,N*-diethylethanamine, and an appropriate catalyst, such as for example tetrakis(triphenylphosphine)palladium. Compounds of formula (I-A-4) can on their turn be converted into a compound of formula (I-A-5) by reaction with potassium fluoride in the presence of a suitable acid such as acetic acid, or by reaction with a suitable base, such as potassium hydroxide, in the presence of a suitable reaction-inert solvent, such as an alcohol, e.g. methanol and the like.

Compounds of formula (I-A-2) can also be converted into a compound of formula (I-A-6) by reaction with an intermediate of formula (IX) in the presence of CuI, a suitable base, such as for example *N,N*-diethylethanamine, and a suitable catalyst such as tetrakis(triphenylphosphine)palladium.

Compounds of formula (I-A-2) can also be converted into a compound wherein R^2 is C_{1-6}alkyl, said compound being represented by formula (I-A-8) in the presence of a suitable alkylating agent, such as for example $Sn(C_{1-6}alkyl)_4$, or into a compound wherein R^2 is C_{2-6}alkenyl, said compound being represented by formula (I-A-9) in the presence of a suitable alkenylating agent, such as for example $Sn(C_{2-6}alkenyl)(C_{1-6}alkyl)_3$, both reactions in the presence of a suitable catalyst, such as for example tetrakis(triphenylphosphine)palladium and a reaction-inert solvent, such as for example toluene or dioxane.

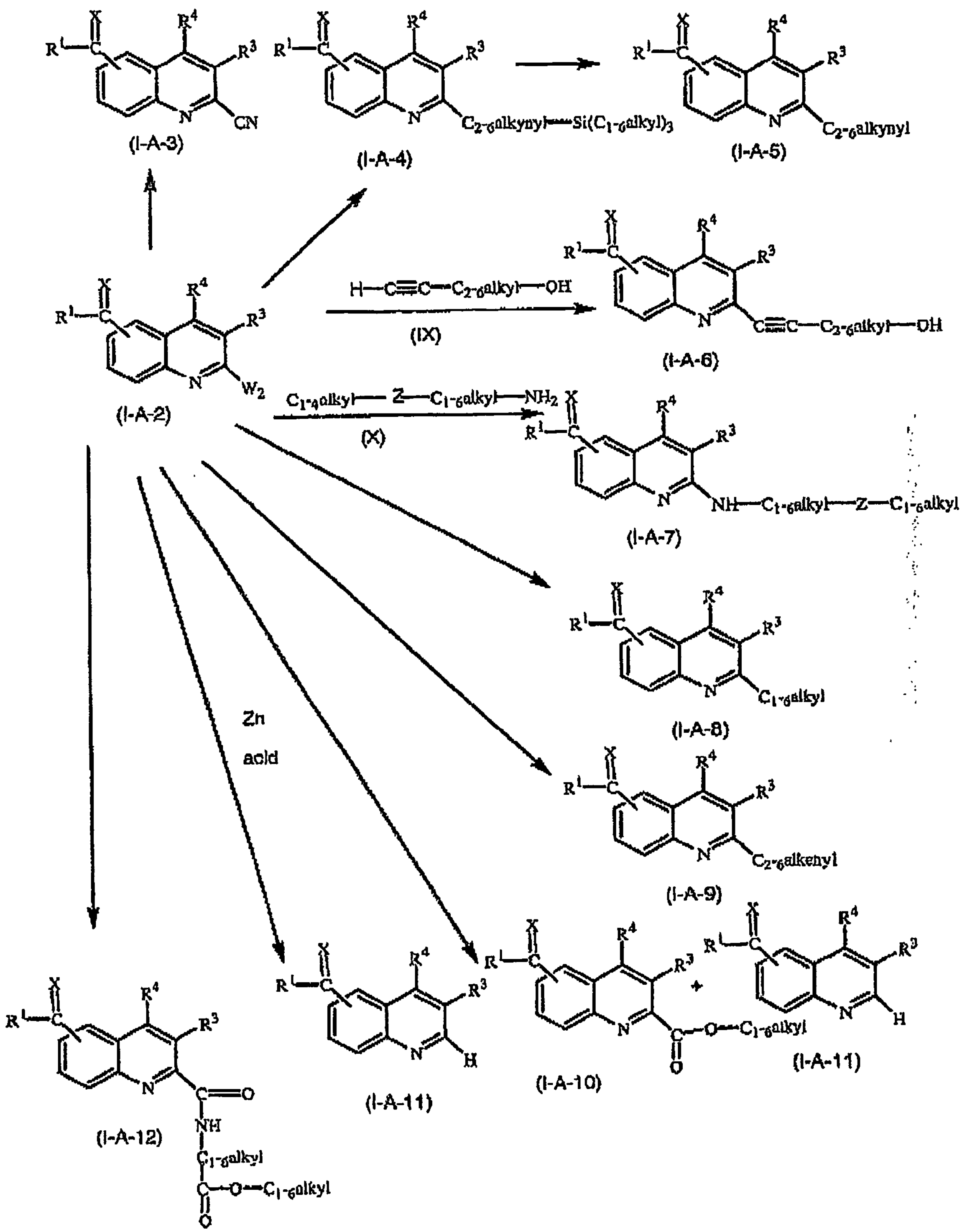
Compounds of formula (I-A-2) can also be converted into a compound of formula (I-A-7) wherein Z represents O or S, by reaction with an intermediate of formula (X) optionally in the presence of a suitable base such as dipotassium carbonate and a reaction-inert solvent, such as *N,N*-dimethyl formamide.

Compounds of formula (I-A-2) can also be converted into a compound of formula (I-A), wherein R^2 is C_{1-6}alkyloxycarbonyl, said compound being represented by formula (I-A-10) and a compound of formula (I-A), wherein R^2 is hydrogen, said compound being represented by formula (I-A-11), by reaction with a suitable alcohol of formula
C_{1-6}alkylOH and CO in the presence of a suitable catalyst, such as for example palladium(II)acetate, triphenylphosphine, a suitable base such as dipotassium carbonate and a reaction-inert solvent, such as *N,N*-dimethylformamide.

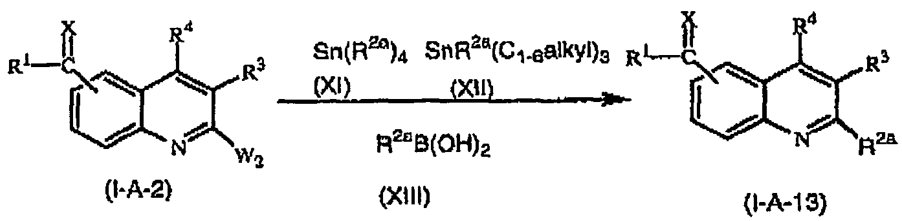
Compounds of formula (I-A-11) can also be prepared by reacting a compound of formula (I-A-2) with Zn in the presence of a suitable acid such as acetic acid.

Compounds of formula (I-A-2) can also be converted into a compound of formula (I-A), wherein R^2 is aminocarbonyl substituted with C_{1-6}alkyloxycarbonylC_{1-6}alkyl, said compound being represented by formula (I-A-12), by reaction with an intermediate of formula H_2N-C_{1-6}alkyl-C(=O)-O-C_{1-6}alkyl in the presence of CO, a suitable catalyst such as tetrakis(triphenylphosphine)palladium, a suitable base, such as for example

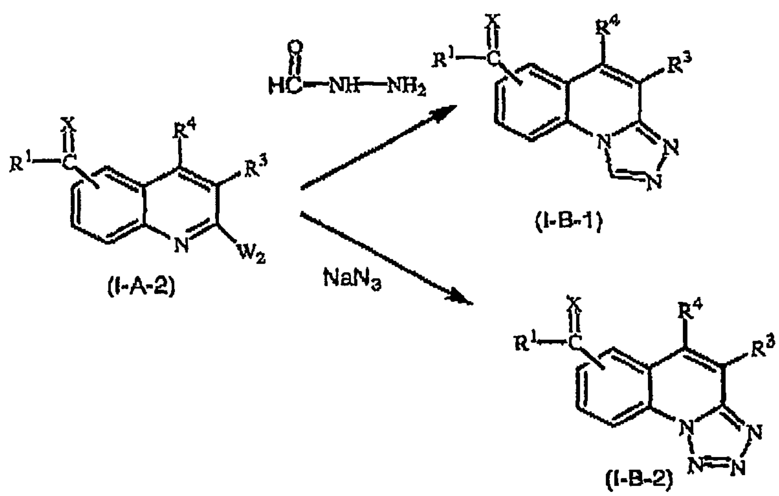
N,N-diethylethanamine, and a suitable reaction-inert solvent, such as for example toluene.


(I-A-3)
(I-A-4)
(I-A-5)
(I-A-2)
H—C≡C—C2-6alkyl—OH
(IX)
(I-A-6)
C1-4alkyl—Z—C1-6alkyl—NH2
(X)
(I-A-7)
(I-A-8)
(I-A-9)
Zn
acid
(I-A-12)
(I-A-11)
(I-A-10)
(I-A-11)

Compounds of formula (I-A-2) can also be converted into a compound of formula (I-A) wherein R^2 is aryl or a heterocycle selected from the group described in the definition of R^2 hereinabove, said R^2 being represented by R^{2a} and said compound by formula (I-A-13) by reaction with an intermediate of formula (XI), (XII) or (XIII) in the presence of a suitable catalyst such as for example tetrakis(triphenylphosphine)palladium and a suitable reaction-inert solvent, such as for example dioxane.

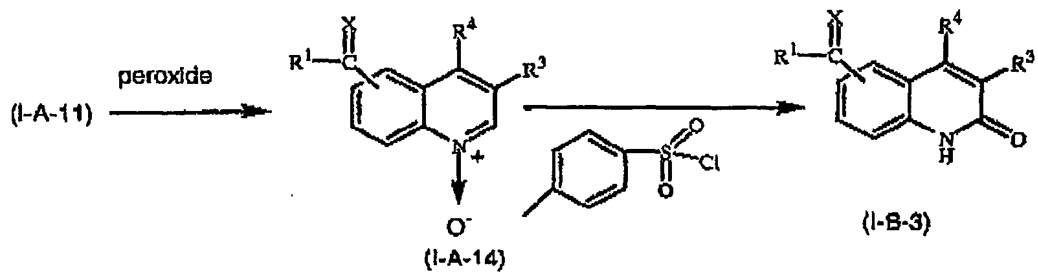


Compounds of formula (I-A-2) can also be converted into a compound of formula (I-B), wherein Y and R^5 are taken together to form a radical of formula (b-1) or (b-2), said compound being represented by formula (I-B-1) or (I-B-2), by reaction with hydrazincarboxaldehyde or sodium azide in a suitable reaction-inert solvent, such as an alcohol, e.g. butanol, or *N,N*-dimethylformamide.

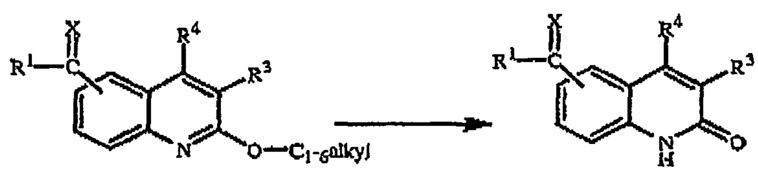


Compounds of formula (I-A-11) can be converted into the corresponding N-oxide, represented by formula (I-A-14), by reaction with a suitable peroxide, such as 3-chloro-benzenecarboperoxoic acid, in a suitable reaction-inert solvent, such as for

example methylene chloride. Said compound of formula (I-A-14) can further be converted into a compound of formula (I-B), wherein R^5 is hydrogen, said compound being represented by formula (I-B-3), by reaction with 4-methyl-benzene sulfonyl chloride in the presence of a suitable base, such as for example dipotassium carbonate and a suitable reaction-inert solvent, such as for example methylene chloride.

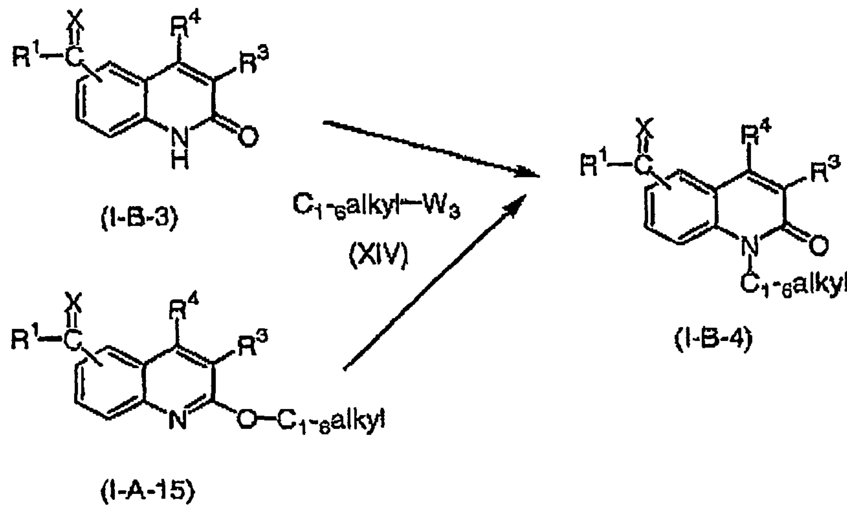


Compounds of formula (I-B-3) can also be prepared from a compound of formula (I-A), wherein R^2 is C_{1-6}alkyloxy, said compound being represented by formula (I-A-15), by reaction with a suitable acid, such as hydrochloric acid, in the presence of a suitable reaction-inert solvent, such as for example tetrahydrofuran.

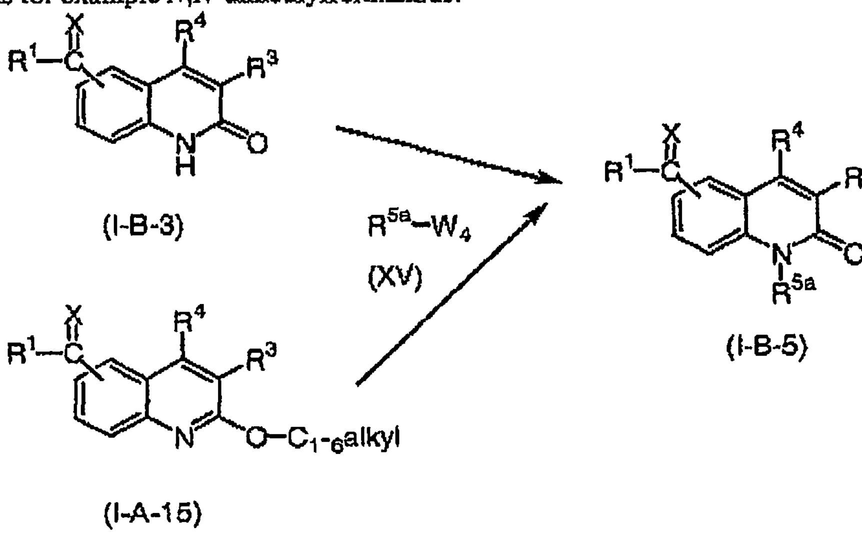


(I-A-15) (I-B-3)

Compounds of formula (I-B-3) can be converted into a compound of formula (I-B), wherein R^5 represents C_{1-6}alkyl, said compound being represented by formula (I-B-4), by reaction with an appropriate alkylating agent, such as for example an intermediate of formula (XIV), wherein W_3 represents a suitable leaving group such as a halo atom e.g. iodo, in the presence of potassium tert. butoxide and in the presence of a suitable reaction-inert solvent, such as for example tetrahydrofuran.

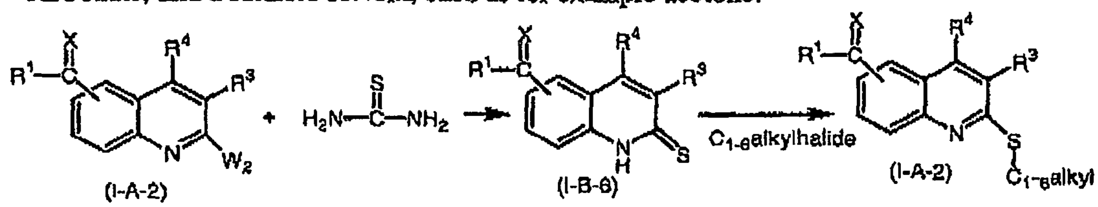


Compounds of formula (I-B-3) can also be converted into a compound of formula (I-B), wherein R^5 is C_{1-6}alkyloxycarbonylC_{1-6}alkyl or arylC_{1-6}alkyl, said R^5 being represented by R^{5a} and said compound being represented by formula (I-B-5), by reaction with an intermediate of formula (XV), wherein W_4 represents a suitable leaving group, such as a halo atom, e.g. bromo, chloro and the like, in the presence of a suitable base, such as for example sodium hydride and a suitable reaction-inert solvent, such as for example *N,N*-dimethylformamide.

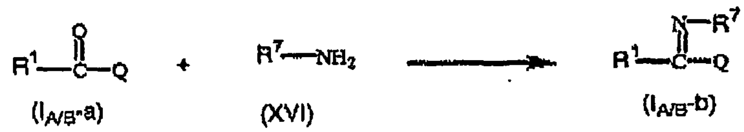


Compounds of formula (I-A-2) can also be converted into a compound of formula (I-B), wherein R^5 is hydrogen and Y is S, said compound being represented by formula (I-B-6), by reaction with H_2N-C(=S)-NH_2 in the presence of a suitable base, such as potassium hydroxide, and a suitable reaction-inert solvent, such as an alcohol, for example ethanol, or water. Compounds of formula (I-B-6) can further be converted

into a compound of formula (I-A), wherein R^2 is C_{1-6}alkylthio, said compound being represented by formula (I-A-16), by reaction with a suitable C_{1-6}alkylhalide, such as for example C_{1-6}alkyliodide, in the presence of a suitable base, such as dipotassium carbonate, and a suitable solvent, such as for example acetone.



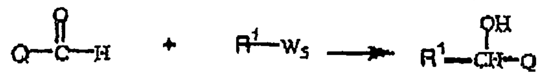
Compounds of formula ($I_{A/B}$-a) can be converted into a compounds of formula (I-A) or (I-B), wherein X is N-R^7, said compound being represented by formula ($I_{A/B}$-b), by reaction with an intermediate of formula (XVI), optionally in the presence of a suitable base, such as for example *N,N*-diethylethanamine, and in the presence of a suitable reaction-inert solvent, such as an alcohol, e.g. ethanol.



As already indicated in the preparation procedure of compounds of formula (I-A-13) described above, the compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

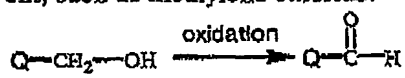
Some of the intermediates and starting materials used in the above reaction procedures are commercially available, or may be synthesized according to procedures already described in the literature.

Intermediates of formula (II) may be prepared by reacting an intermediate of formula (XVII) with an intermediate of formula (XVIII), wherein W_5 represents a suitable leaving group such as a halo atom, e.g. chloro, bromo and the like, in the presence of magnesium, diethylether and a suitable reaction-inert solvent, such as diethylether.



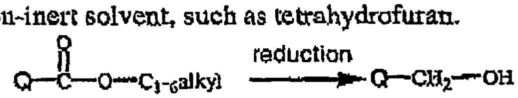
(XVII) (XVIII) (II)

Intermediates of formula (XVII) may be prepared by oxidizing an intermediate of formula (XIX) in the presence of a suitable oxidizing agent, such as MnO_2, and a suitable reaction-inert solvent, such as methylene chloride.



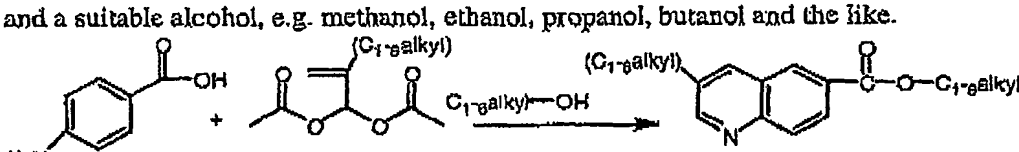
(XIX) (XVII)

Intermediates of formula (XIX) can be prepared by reducing an intermediate of formula (XX) in the presence of a suitable reducing agent such as lithium aluminium hydride, and a suitable reaction-inert solvent, such as tetrahydrofuran.



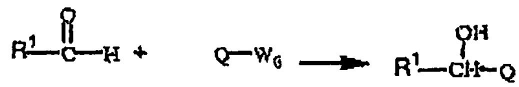
(XX) (XIX)

Intermediates of formula (XX), wherein Q represents a quinoline moiety optionally substituted in position 3 with C_{1-6}alkyl and wherein the carbonyl moiety is placed in position 6, said intermediates being represented by formula (XX-a), can be prepared by reacting an intermediate of formula (XXI) with an intermediate of formula (XXII) in the presence of sodium 3-nitro-benzene sulfonate, a suitable acid, such as sulfuric acid, and a suitable alcohol, e.g. methanol, ethanol, propanol, butanol and the like.



(XXI) (XXII) (XX-a)

Alternatively, intermediates of formula (II) can also be prepared by reacting an intermediate of formula (XXIII) with an intermediate of formula (XXIV), wherein W_6 is a suitable leaving group, such as a halo atom, e.g. bromo, chloro and the like, in the presence of a suitable agent, such as butyl lithium and a suitable reaction-inert solvent, such as tetrahydrofuran.

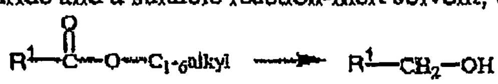


(XXIII) (XXIV) (II)

Intermediates of formula (XXIII) can be prepared by oxidizing an intermediate of formula (XXV) using the Moffatt Pfitzner or Swern oxidation (dimethylsulfoxide adducts with dehydrating agents e.g. DCC, Ac_2O, SO_3, P_4O_{10}, $COCl_2$ or Cl-CO-COCl) in an inert solvent such as methylene chloride.

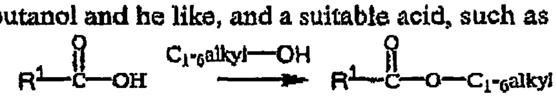
(XXV) (XXIII)

Intermediates of formula (XXV) can be prepared by reducing an intermediate of formula (XXVI) in the presence of a suitable reducing agent, such as for example lithium aluminium hydride and a suitable reaction-inert solvent, such as benzene.



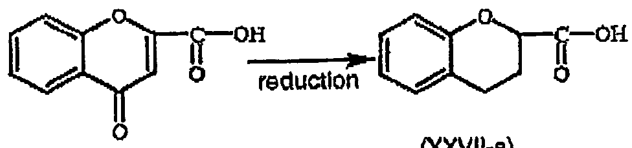
(XXVI) (XXV)

Intermediates of formula (XXVI) can be prepared from an intermediate of formula (XXVII) by esterification in the presence of a suitable alcohol, such as methanol, ethanol, propanol, butanol and he like, and a suitable acid, such as sulfuric acid.



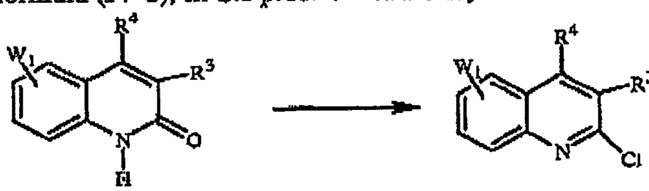
(XXVII) (XXVI)

Intermediates of formula (XXVII), wherein R^1 represents a radical of formula (a-1) with Z_1 being O, Z_2 being CH_2 and n being 1, said intermediates being represented by formula (XXVII-a), can be prepared by reducing an intermediate of formula (XXVIII) in the presence of a suitable reducing agent such as hydrogen, and a suitable catalyst, such as palladium on charcoal, and a suitable acid such as acetic acid. When R^1 of intermediate (XXVII) represents an optionally substituted phenyl moiety, it can also be converted into an optionally substituted cyclohexyl moiety by reduction in the presence of a suitable reducing agent such as rhodium on Al_2O_3, and a suitable reaction-inert solvent, such as tetrahydrofuran.



(XXVIII) (XXVII-a)

Intermediates of formula (IV), wherein Q represents a quinoline moiety substituted in position 2 with halo,e.g. chloro, said intermediates being represented by formula (IV-a), can be prepared by reacting an intermediate of formula (IV), wherein Q represents a quinolinone moiety with R^5 being hydrogen, said intermediate being represented by formula (IV-b), in the presence of $POCl_3$.

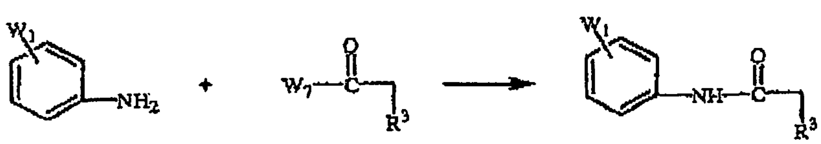


(IV-b) (IV-a)

Intermediates of formula (IV-a), wherein R^4 is hydrogen, said intermediates being represented by formula (IV-a-1), can also be prepared by reacting an intermediate of formula (XXIX) with $POCl_3$ in the presence of *N,N*-dimethylformamide (Vilsmeier-Haack formylation followed by cyclization).

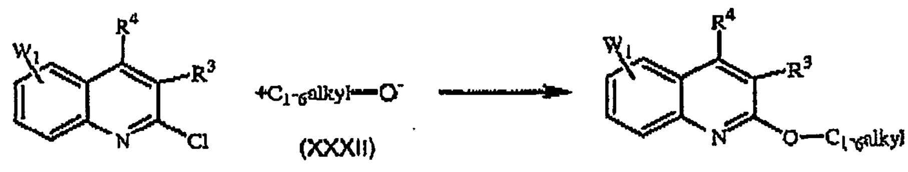
(XXIX) (IV-a-1)

Intermediates of formula (XXIX) may be prepared by reacting an intermediate of formula (XXX) with an intermediate of formula (XXXI), wherein W_7 represents a suitable leaving group, such as a halo atom, e.g. chloro, in the presence of a suitable base, such as for example *N,N*-diethylethanamine, and a suitable reaction-inert solvent, such as methylene chloride.



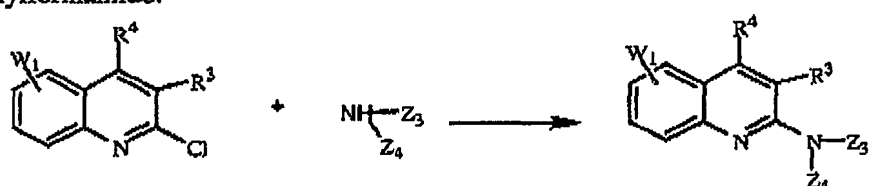
(XXX) (XXXI) (XXIX)

Intermediates of formula (IV-a) can be converted into an intermediate of formula (IV-c) by reaction with an intermediate of formula (XXXII) in the presence of a suitable reaction-inert solvent, such as an alcohol, e.g. methanol and the like.

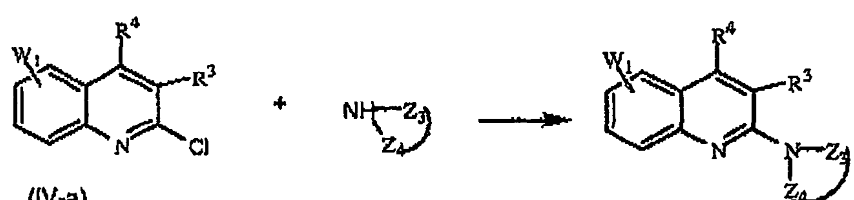


(IV-a) (XXXII) (IV-c)

Intermediates of formula (IV-a) can also be converted into an intermediate of formula (IV-d-1) by reaction with a suitable amine of formula (XXXIII-a), wherein Z_3 and Z_4 each independently represent hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthioC_{1-6}alkyl or into an intermediate of formula (IV-d-2) by reaction with a suitable amine of formula (XXXIII-b), wherein Z_3 and Z_4 are taken together to form a heterocycle as defined hereinabove in the definition of R^2 provided that the heterocycle comprises at least one nitrogen atom, in the presence of a suitable base, such as for example dipotassium carbonate, and a reaction-inert solvent, such as *N,N*-dimethylformamide.



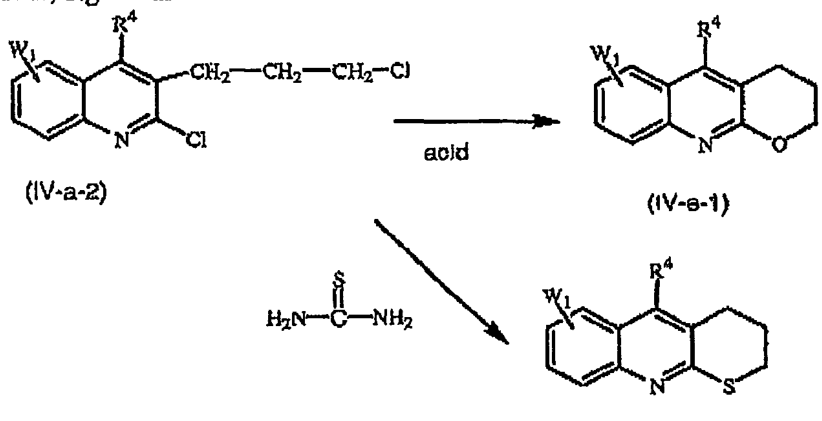
(IV-a) (XXXIII-a) (IV-d-1)



(IV-a) (XXXIII-b) (IV-d-2)

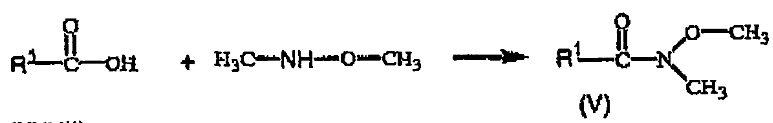
Intermediates of formula (IV-a), wherein R^3 represents CH_2-CH_2-CH_2-Cl, said intermediates being represented by formula (IV-a-2), can also be converted into an intermediate of formula (IV), wherein R^2 and R^3 are taken together to form a bivalent radical of formula –O-CH_2-CH_2-CH_2-, said intermediate being represented by formula (IV-e-1), by reaction with a suitable acid, such as hydrochloric acid and the like. Intermediates of formula (IV-a-2) can also be converted into an intermediate of formula (IV), wherein R^2 and R^3 are taken together to form a bivalent radical of formula

-S-CH_2-CH_2-CH_2-, said intermediate being represented by formula (IV-e-2), by reaction with H_2N-C(=S)-NH_2 in the presence of a suitable reaction-inert solvent, such as an alcohol, e.g. ethanol.



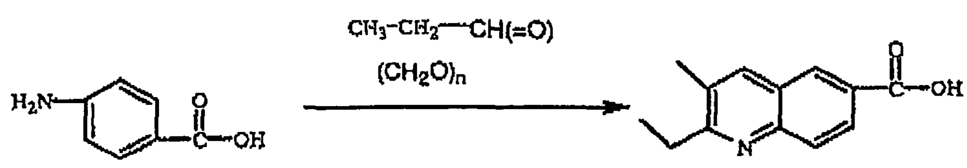
(IV-a-2) (IV-e-1) (IV-e-2)

Intermediates of formula (V) may be prepared by reacting an intermediate of formula (XXVII) with an intermediate of formula CH_3-NH-O-CH_3 in the presence of 1,1'-carbonyldiimidazole and a suitable reaction-inert solvent, such as methylene chloride.



(XXVII) (V)

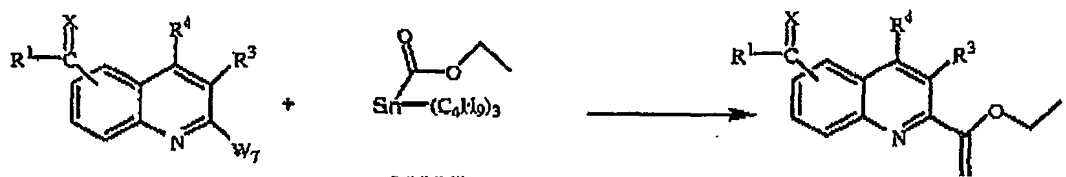
Intermediates of formula (VII), wherein Q represents a quinoline moiety, in particular a quinoline moiety wherein R^2 is ethyl, R^3 is methyl and R^4 is hydrogen, and the carboxyl moiety is placed in position 6, said intermediates being represented by formula (VII-a), can be prepared by reaction an intermediate of formula (XXXIV) in the presence of a suitable aldehyde, such as CH_3-CH_2-CH(=O), $(CH_2O)_n$, $ZnCl_2$, $FeCl_3$ and a suitable reaction-inert solvent, such as an alcohol, for example ethanol.



(XXXIV) (VII-a)

Intermediates of formula (VIII) can be prepared by reacting an intermediate of formula (XXXV) with an intermediate of formula (XXXVI) in the presence of a suitable

catalyst, such as for example tetrakis(triphenylphosphine)palladium and a suitable reaction-inert solvent, such as for example dioxane.



(XXXV) (XXXVI) (VIII)

Still some other preparations can be devised, some of them are disclosed further in this application with the Examples.

Pure stereoisomeric forms of the compounds and the intermediates of this invention may be obtained by the application of art-known procedures. Diastereomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g. liquid chromatography using chiral stationary phases. Enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids. Alternatively, enantiomers may be separated by chromato-graphic techniques using chiral stationary phases. Said pure stereoisomeric forms may also be derived from the corresponding pure stereoisomeric forms of the appropriate starting materials, provided that the reaction occurs stereoselectively or stereospecifically. Preferably, if a specific stereoisomer is desired, said compound will be synthesized by stereoselective or stereospecific methods of preparation. These methods will advantageously employ chirally pure starting materials. Stereoisomeric forms of the compounds of formula (I) are obviously intended to be included within the scope of the invention.

A stereoisomer of a compound of formula (I-A) or (I-B) such as a *cis* form, may be converted into another stereoisomer such as the corresponding *trans* form by reacting the compound with a suitable acid, such as hydrochloric acid, in the presence of a suitable reaction-inert solvent, such as for example tetrahydrofuran.

The mGluR1 antagonistic activity of the present compounds can be demonstrated in the Signal transduction on cloned rat mGluR1 in CHO cells test and the Cold allodynia test in rats with a Bennett ligation, as described hereinafter.

Due to their mGluR antagonistic activity, more in particular their Group I mGluR antagonistic activity and even more in particular, their mGluR1 antagonistic activity, the compounds of formula (I-A) or (I-B), their *N*-oxides, pharmaceutically acceptable addition salts, quaternary amines and stereochemically isomeric forms are useful in the treatment or prevention of glutamate-induced diseases of the central nervous sytem. Diseases in which a role for glutamate has been demonstrated include drug addiction or abstinence (dependence, opioid tolerance, opioid withdrawal), hypoxic, anoxic and ischemic injuries (ischemic stroke, cardiac arrest), pain (neuropathic pain, inflammatory pain, hyperalgesia), hypoglycemia, diseases related to neuronal damage, brain trauma, head trauma, spinal cord injury, myelopathy, dementia, anxiety, schizophrenia, depression, impaired cognition, amnesia, bipolar disorders, conduct disorders, Alzheimer's disease, vascular dementia, mixed (Alzheimer's and vascular) dementia, Lewy Body disease, delirium or confusion, Parkinson's disease, Huntington's disease, Down syndrome, epilepsy, aging, Amyotrophic Lateral Sclerosis, multiple sclerosis, AIDS (Acquired Immune Deficiency Syndrome) and AIDS related complex (ARC).

The present invention also provides compositions for the administration to mamals, in particular humans, in particular for diagnostic reasons, more in particular for imaging an organ comprising a therapeutically effective amount of a radiolabelled compound of formula (I-A)* or (I-B)* and a pharmaceutically acceptable carrier or diluent.

Therefore, the compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, a therapeutically effective amount of a particular compound, in base or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, topically, percutaneously or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, emulsions, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills,

capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. As appropriate compositions for topical application there may be cited all compositions usually employed for topically administering drugs e.g. creams, gel, dressings, shampoos, tinctures, pastes, ointments, salves, powders and the like. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, suppositories, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The diagnostically effective dose or frequency of administration depends on the particular compound of formula (I-A)* or (I-B)* used and the particular condition of the mamal being treated, as is well known to those skilled in the art.

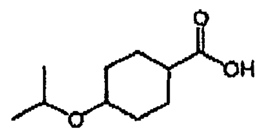
The following examples are intended to illustrate and not to limit the scope of the present invention.

Experimental part

Hereinafter, "DMF" is defined as *N,N*-dimethylformamide, "DIPE" is defined as diisopropylether, "DMSO" is defined as dimethylsulfoxide, "BHT" is defined as 2,6-bis(1,1-dimethylethyl)-4-methylphenol, and "THF" is defined as tetrahydrofuran.

A. Preparation of the intermediates

Example A1

Preparation of  (interm. 1)

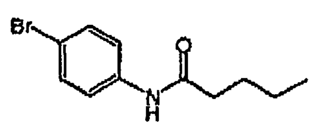
A mixture of 4-(1-methylethoxy)benzoic acid (0.083 mol) and Rh/Al_2O_3 5% (10g) in THF (220ml) was hydrogenated at 50°C (under 3 bar pressure of H_2) for 1 night. The mixture was filtered over celite, washed with THF and evaporated. Yield: 16g of intermediate 1 (100%).

Example A2

Preparation of 2-ethyl-3-methyl-6-quinolinecarboxylic acid (interm. 2)

A mixture of 4-aminobenzoic acid (0.299 mol) in ethanol (250ml) was stirred at room temperature. $ZnCl_2$ (0.0367 mol) and $(CH_2O)_n$ (10g) were added. $FeCl_3.6H_2O$ (0.5 mol) was added portionwise and the temperature rised till 60-65°C. Propanal (30ml) was added dropwise over a 2 hours period. The mixture was refluxed for 2 hours and kept at room temperature for 12 hours. The mixture was poured into water and filtered through celite. The filtrate was acidified till pH=7 with HCl 6N and the mixture was evaporated till dryness. The residue was used without further purification. Yield : 56.1g of 2-ethyl-3-methyl-6-quinolinecarboxylic acid (interm. 2).

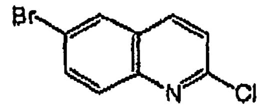
Example A3

Preparation of  (interm. 3)

Pentanoyl chloride (0.2784 mol) was added at 5°C to a mixture of 4-bromobenzenamine (0.232 mol) and *N,N*-diethylethanamine (0.2784 mol) in CH_2Cl_2 (400ml). The mixture was stirred at room temperature overnight, poured out into water and extracted with CH_2Cl_2. The organic layer was separated, washed with a concentrated NH_4OH solution and water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (60g) was crystallized from diethylether. The precipitate was

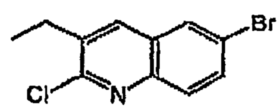
filtered off and dried. The residue (35g, 63%) was taken up in CH_2Cl_2. The organic layer was separated, washed with a 10% K_2CO_3 solution, washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. Yield: 30g of intermediate (3) (54%).

Example A4

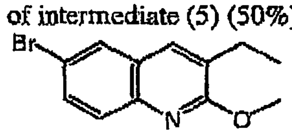
Preparation of  (interm. 4)

A mixture of 6-bromo-2(1*H*)-quinolinone (0.089 mol) in $POCl_3$ (55ml) was stirred at 60°C overnight, then at 100°C for 3 hours and the solvent was evaporated. The residue was taken up in CH_2Cl_2, poured out into ice water, basified with NH_4OH conc., filtered over celite and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. Yield: 14.5g of intermediate (4) (67%).

Example A5

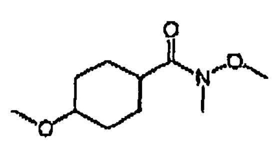
a) Preparation of  (interm. 5)

DMF (37ml) was added dropwise at 10°C under N_2 flow to $POCl_3$ (108ml). After complete addition, the mixture was allowed to warm to room temperature. *N*-(4-bromophenyl)butanamide (0.33 mol) was added portionwise. The mixture was stirred at 85°C overnight, then allowed to cool to room temperature and poured out on ice (exothermic reaction). The precipitate was filtered off, washed with a small amount of water and dried (vacuum). The residue was washed with EtOAc/diethyl ether and dried. Yield: 44.2g of intermediate (5) (50%).

b) Preparation of  (interm. 6)

A mixture of intermediate (5) (0.162 mol) in methanol (600ml), and a solution of methanol sodium salt in methanol at 35% (154ml) was stirred and refluxed overnight. The mixture was poured out on ice. The precipitate was filtered off, washed with a small amount of water and taken up in CH_2Cl_2. K_2CO_3 10% was added and the mixture was extracted with CH_2Cl_2. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. Yield: 31.9g of intermediate (6) (74%).

Example A6

Preparation of  (interm. 7)

1,1'-Carbonylbis-1*H*-imidazole (0.074 mol) was added portionwise to a mixture of 4-methoxycyclohexanecarboxylic acid (0.063 mol) in CH_2Cl_2 (200ml). The mixture

was stirred at room temperature for 1 hour. Then *N*-methoxymethanamine (0.074 mol) was added. The mixture was stirred at room temperature overnight, poured out into H_2O and extracted with CH_2Cl_2. The organic layer was separated, washed several times with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. Yield: 12.6g of interm. 7.

Example A7

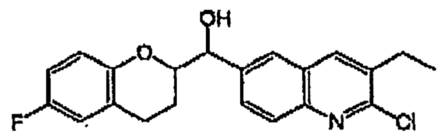
a) A mixture of 6-fluoro-4-oxo-4*H*-1-benzopyran-2-carboxylic acid (0.30mol) in acetic acid (400ml) was hydrogenated with Pd/C (3g) as a catalyst. After uptake of H_2 (3 equiv), the catalyst was filtered off. The filtrate was evaporated. The residue was stirred in petroleum ether. The precipitate was filtered off and dried (vacuum; 70°C). After recrystallization from $CHCl_3/CH_3OH$, the precipitate was filtered off and dried (vacuum; 80°C and high vacuum; 85°C). Yield: 8.8 g of 6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-carboxylic acid (interm. 8) (15.0%).

b) A mixture of intermediate (8) (0.255 mol) in ethanol (400ml) and H_2SO_4 (5ml) was stirred and refluxed for 8 hours. The solvent was evaporated till dryness. The residue was dissolved in CH_2Cl_2. The organic layer was separated, washed with K_2CO_3 10%, dried ($MgSO_4$), filtered and the solvent was evaporated. Yield: 45g of ethyl 6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-carboxylate (interm. 9) (79%).

c) Reaction under N_2. A mixture of sodium bis(2-methoxyethoxy)aluminumhydride, 70 wt % solution in methylbenzene 3.4M (0.44 mol) in benzene (150 ml) (reflux) was added dropwise during 1 hour to a refluxed mixture of interm. 9 (0.22 mol) and benzene (600 ml). After stirring for 2.5 hours at reflux temperature, the mixture was cooled to ±15°C. The mixture was decomposed by adding dropwise ethanol (30 ml) and water (10 ml). This mixture was poured out onto ice/water and this mixture was acidified with concentrated hydrochloric acid. This mixture was extracted with diethyl ether (500 ml). The separated organic layer was washed with water, dried, filtered and the solvent was evaporated. The residue was purified by column chromotoghaphy over silica gel (eluent : $CHCl_3$). The desired fraction was collected and the eluent was evaporated. Yield: 34 g of 6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol (interm. 10) (85%).

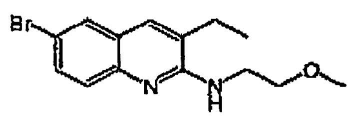
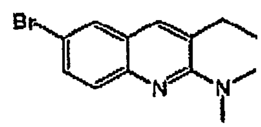
d) Reaction under N_2. To a stirred and cooled (-60°C; 2-propanone/CO_2 bath) mixture of ethanedioyl dichloride (0.1 mol) in CH_2Cl_2 (350 ml) was added sulfinylbis[methane] (30 ml) during 10 minutes. After stirring 10 minutes, a mixture of interm. 10 in CH_2Cl_2 (90 ml) was added during 5 minutes. After stirring for 15 minutes, *N,N*-diethylethanamine (125 ml) was added. When the mixture was warmed up to room temperature, it was poured out in water. The product was extracted with CH_2Cl_2.

The organic layer was wased with water, HCl (1M), water, $NaHCO_3$ (10%) and water, dried and evaporated. The residue was dissolved in diethyl ether, washed with water, dried, filtered and evaporated. The residue was purified by column chromotogbaphy over silica gel (eluent : $CHCl_3$). The desired fraction was collected and the eluent was evaporated. Yield: 21.6 g of 6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-carboxaldehyde (interm. 11) (67%).

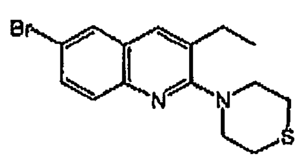
e) Preparation of  (interm. 12)

nButyllithium 1.6M (0.056 mol) was added slowly at -70°C to a solution of intermediate (5) (0.046 mol) in THF (100ml). The mixture was stirred at -70°C for 30 minutes. A suspension of interm. 11 (0.056 mol) in THF (100ml) was added slowly. The mixture was stirred at -70°C for 1 hour, then brought to room temperature, poured out into H_2O and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (21g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/10; 15-35μm). The pure fractions were collected and the solvent was evaporated. Yield: 9.5g of interm. 12 (55%).

<u>Example A8</u>

a) Preparation of  (interm. 13) and  (interm. 14)

A mixture of intermediate (5) (0.1127 mol), 2-methoxyethanamine (0.2254 mol) and K_2CO_3 (0.2254 mol) in DMF (500ml) was stirred at 120°C for 15 hours and then cooled. The solvent was evaporated. The residue was taken up in CH_2Cl_2 and H2O. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (33.53g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99.5/0.5; 15-40 μm). Two fractions were collected and their solvents were evaporated. Yield: 5.7g of interm. 14 (38%) and interm. 13 (34%).

b) Preparation of  (interm. 15)

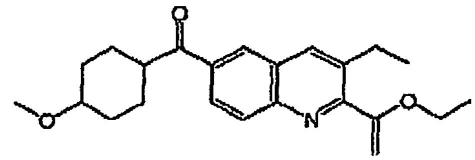
A mixture of intermediate (5) (0.0751 mol), thiomorpholine (0.0891 mol) and K_2CO_3 (0.15 mol) in DMF (200ml) was stirred at 120°C for 12 hours. The solvent was

evaporated till dryness. The residue was taken up in CH_2Cl_2 and H_2O. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (26g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/20; 20-45 μm). Two fractions were collected and their solvents were evaporated. The two fractions were combined. Yield: 9.4g of interm. 15 (37%); mp. 82°C.

Example A9

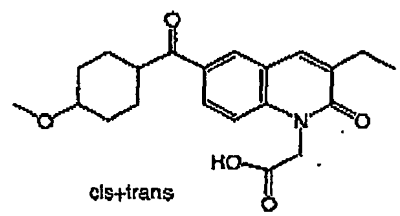
a) 4-Aminobenzoic acid (0.219 mol) was added to a solution of sodium 3-nitrobenzenesulfonate (0.118 mol) in H_2SO_4 70% (230ml) and the mixture was stirred and refluxed. 2-propene-1,1-diol, 2-methyl-, diacetate (0.216 mol) was added dropwise and the mixture was refluxed for 4 hours. Ethanol (200ml) was added and the mixture was stirred at 80°C for 48 hours. The mixture was evaporated, the residue was poured into ice water/NH_4OH and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/2-propanol 99/1). The pure fractions were collected and evaporated. Yield : 21g of ethyl 3-methyl-6-quinolinecarboxylate (interm. 16) (45%).
b) Interm. 16 (0.098 mol) in THF (270ml) was added at 0°C to a solution of $LiAlH_4$ (0.098 mol) in THF under N_2. When the addition was complete, water (10ml) was added. The precipitate was filtered off and washed with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered off and evaporated. The product was used without further purification. Yield : 16.71g of 3-methyl-6-quinolinemethanol (interm. 17).
c) MnO_2 (0.237 mol) was added to a solution of interm. 17 (0.096 mol) in CH_2Cl_2 (200ml) and the mixture was stirred at room temperature for 12 hours. The mixture was filtered through celite and the filtrate was stirred again with MnO_2 (20g) for 12 hours. MnO_2 (10g) was added again. The mixture was stirred for 12 hours. The mixture was filtered through celite and evaporated. The product was used without further purification. Yield : 11.71g of 3-methyl-6-quinolinecarboxaldehyde (71%) (interm. 18).
d) A solution of bromocyclohexyl (0.14 mol) in 1,1'-oxybisethane (50ml) and Mg turnings (50ml) was added at 10°C to a mixture of THF (0.14 mol) in 1,1'-oxybisethane (10ml). A solution of interm. 18 (0.07 mol) in Mg turnings (100ml) was added carefully at 5°C, the mixture was poured into ice water and extracted with EtOAc. Yield : 11.34g of (±)-α-cyclohexyl-3-methyl-6-quinolinemethanol (63%) (interm. 19).

Example A10

Preparation of  (interm. 20)

A mixture of compound (5) (0.001507 mol), tributyl(1-ethoxyethenyl)stannane (0.00226 mol) and $Pd(PPh_3)_4$ (0.000151 mol) in 1,4-dioxane (5ml) was stirred at 80°C for 3 hours. Water was added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. This product was used without further purification. Yield: 1.4g of interm. 20.

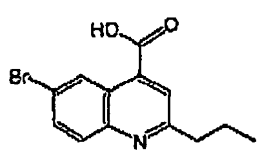
Example A11

Preparation of 

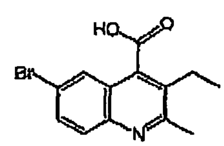
(interm. 21)

A mixture of compound (45) (prepared according to B6) (0.00125 mol) in NaOH 3N (5 ml) and iPrOH (1.7 ml) was stirred at room temperature overnight, then poured out into H_2O, acidified with HCl 3N and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was taken up in diethyl ether. The precipitate was filtered off and dried. Yielding: 0.26 g of intermediate 23 (56%). (mp.: 232°C)

Example A12

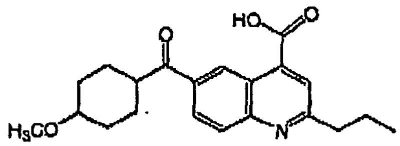
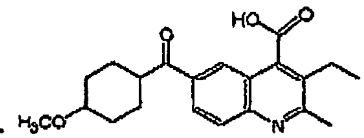
a. Preparation of 

(interm. 22)



(interm. 23)

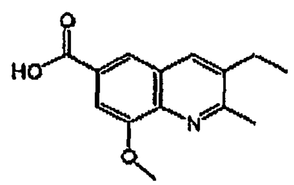
A mixture of 5-bromo-1H-indole-2,3-dione (0.221 mol) in NaOH 3N (500 ml0 was stirred at 80°C for 30 minutes, brought to room temperature and 2-pentanone (0.221 mol) was added. The mixture was stirred and refluxed for 1 hour and 30 minutes and acidified with AcOH until pH=5. The precipitate was filtered, washed with water and dried. Yielding 52.3 g of intermediate 24 and intermediate 25. (Total yielding: 80%).

b. Preparation of  

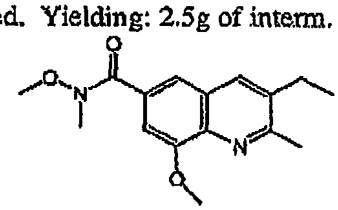
(interm. 24) (interm. 25)

nBuLi 1.6 M (0.0816 mol) was added dropwise at –78°C to a suspension of intermediate 25 (0.034 mol) and intermediate 26 (0.034 mol) in THF (300 ml) under N_2 flow. The mixture was stirred at –78°C for 30 minutes. nBuLi 1.6M (0.0816 mol) was added dropwise. The mixture was stirred for 1 hour. A mixture of intermediate 9 (0.102 mol) in THF (250 ml) was added slowly. The mixture was stirred for –78°C to –20°C, poured out into H_2O/HCl 3N and extracted with EtOAc. The organic layer was separated, dired ($MgSO_4$), filtered, and the solvent was evaporated till dryness. Yielding: 20.89 g of compound intermediate 26 and intermediate 27 (86%).

<u>Example A13</u>

a. Preparation of  (interm. 26)

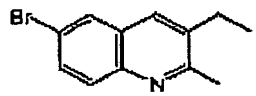
4-amino-3-methoxybenzoic acid (0.054 mol) was added portionwise at room temperature to a solution of 3-chloro-2-ethyl-2-butenal (0.065 mol) in AcOH (100ml). The mixture was stirred and refluxed for 8 hours and evaporated to dryness. The residue was taken up in CH_2Cl_2, water was added and the solution was basified by Et_3N. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue was crystallized from 2-propanone. The precipitate was filtered off and dried. Yielding: 2.5g of interm. 26 (18%).

b. Preparation of  (interm. 27)

CDI (0.012 mol) was added at room temperature to a solution of interm. 26 (0.011 mol) in CH_2Cl_2 (30ml). The mixture was stirred at room temperature for 1 hour. methoxyaminomethyl (0.012 mol) was added and the mixture was stirred at room temperature for 8 hours. H_2O was added. A precipitate was filtered off. The filtrate was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered, and

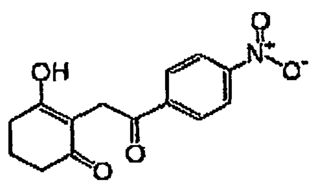
the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.95g of interm. 27 (31%) (mp.:148°C).

Example A14

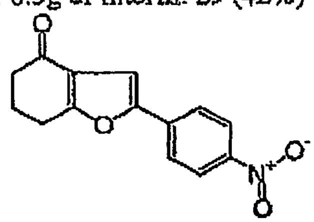
Preparation of  (interm. 28)

4-Bromobenzenamine (0.034 mol) was added at room temperature to a solution of 3-chloride-2-ethyl-2-butanal (0.041 mol) in AcOH (60 ml). The mixture was stirred and refluxed for 8 hours, brought to room temperature and evaporated to dryness. The product was crystallized from EtOAc. The precipitate was filtered, washed with K2CO3 10% and taken up in CH2Cl2. The organic layer was separated, dried (MgSO4), filtered, and the solvent was evaporated. Yielding: 4,6 g of interm. 28 (54%).

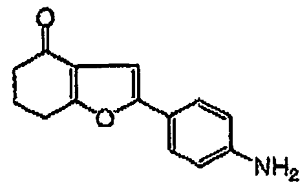
Example A15

a. Preparation of  (interm. 29)

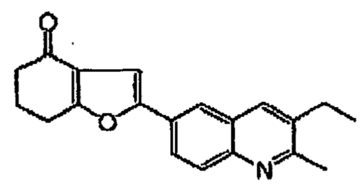
A solution of KOH (0.326 mol) in H_2O (150ml) was added slowly at 5°C to a solution of 1,3-cyclohexanedione (0.268 mol) in H_2O (150ml). The temperature must not reach 12 °C. KI (2g) then 2-bromo-1-(4-nitrophenyl)ethanone (0.294 mol) were added portionwise. The mixture was stirred at room temperature for 48 hours. The precipitate was fitered, washed with H_2O then with diethyl ether and dried. Yielding: 63g (85%). A part of this fraction (1g) was crystallized from EtOH. The precipitate was filtered off and dried. Yielding: 0.5g of interm. 29 (42%) (mp.: 100°C).

b. Preparation of  (interm. 30)

A mixture of interm. 29 (0.145 mol) in H_2SO_4 (40ml) was stirred at room temperature for 1 hour, poured out into ice, basified with NH_4OH and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue was crystallized from EtOH. The precipitate was filtered off and dried. Yielding: 31g (58%). A part of this fraction (1g) was crystallized from EtOH. The precipitate was filtered off and dried. Yielding: 0.7g of interm. 30 (58%) (mp.:200°C).

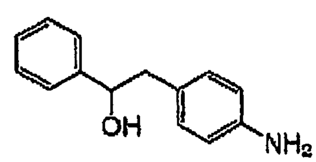
c. Preparation of  (interm. 31)

A mixture of interm. 30 (0.039 mol), Raney Ni (10g) in EtOH (100ml) was hydrogenated at room temperature under a 3 bar pressure for 1 hour. The mixture was filtered over celite and washed with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (9.5g) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 4.6g (52%). The filtrate was evaporated. The residue (2.7g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH; 99/1; 15-40μm). Two fractions were collected and the solvent was evaporated. Yielding: 1.6g F1 and 1.2g F2. F2 was crystallized from EtOH. The precipitate was filtered off and dried. Yielding: 0.24g of interm. 31 (2%) (mp.:202°C).

d. Preparation of  (interm. 32)

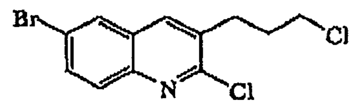
Interm. 30 (0.02 mol) was added at room temperature to a solution of 3-chloro-2-ethyl-2-butenal (0.04 mol) in AcOH (50ml). The mixture was stirred and refluxed for 4 hours. The solvent was evaporated till dryness. The residue was crystallized from EtOAc. The precipitate was filtered off and dried. The residue was taken up in CH_2Cl_2. The mixture was basified with K_2CO_3 10% and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue was crystallized from EtOH. The precipitate was filtered off and dried. Yielding: 2.5g of interm. 32 (40%).

<u>Example A16</u>

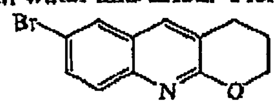
Preparation of  (interm. 33)

A mixture of 2-(4-nitrophenyl)-1-phenylethanone (0.083 mol) and Raney Ni (20g) in EtOH (200ml) was hydrogenated at room temperature for 1 hour under a 3 bar pressure, then filtered over celite, washed with CH_2Cl_2/CH_3OH and dried. Yielding: 17.5g of interm. 33 (97%).

Example A17

a. Preparation of  (interm. 34)

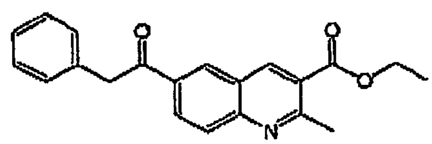
DMF (12.4ml) was added dropwise at 5°C to $POCl_3$ (0.7536 mol). 4'-bromo-5-chlorovaleranilide (0.1032 mol) was added and the mixture was stirred at 75°C for 6 hours, cooled at room temperature and poured out into ice water. The insoluble was filtered, washed with water and dried. Yielding: 25.7g of intermediate 34 (78%).

b. Preparation of  (interm. 35)

A mixture of intermediate 34 (0.094 mol) in HCl 6N (250ml) was stirred and refluxed for 2 days, cooled, poured out on water (100ml) and neutralyzed with NH_4OH (concentrated). The insoluble was filtered and washed with water then with EtOH. Yielding: 19g. The filtrate was evaporated. The residue (9.4g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99.25/0.75; 15-35μm). One fraction was collected and the solvent was evaporated. Yielding: 8g of intermediate 35 (32%).

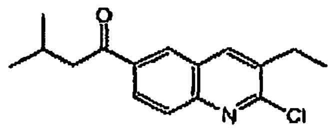
B. Preparation of the non-radioactive compounds

Example B1

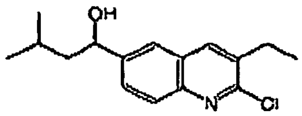
Preparation of  (compound 306)

$POCl_3$ (0.024 mol) was added slowly at 5°C to DMF (0.024 mol). The mixture was stirred at room temperature for 30 minutes, then cooled to 5°C. 3-Oxo-butanoic acid ethyl ester (0.024 mol) was added slowly. The mixture was stirred at 5°C for 30 minutes. 1-(4-aminophenyl)-2-phenylethanone (0.024 mol) was added portionwise. The mixture was stirred at 90°C for 3 hours and dissolved in CH_2Cl_2. Ice water was added. The mixture was basified with NH_4OH and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue was crystallized from 2-propanone/diethyl ether. The precipitate was filtered off and dried. Yielding: 0.9 g of compound 306 (11%) (mp.:136°C).

Example B2

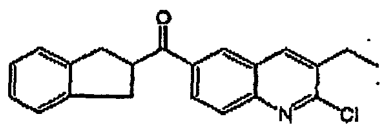
Preparation of  (compound 2)

$KMnO_4$ (10g) was added portionwise at room temperature to a solution of

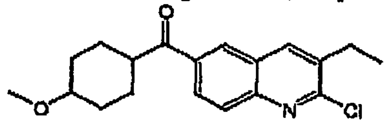
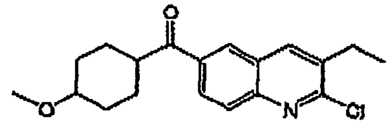
 (prepared according to example A7.e) (0.022 mol)

in tris(dioxa-3,6-heptyl)amine (1ml) and CH_2Cl_2 (100ml). The mixture was stirred at room temperature for 8 hours, filtered over celite, washed with CH_2Cl_2 and dried. The residue (6g, 100%) was crystallized from diethyl ether/petroleum ether. The precipitate was filtered off and dried. Yield: 2g of compound (2) (33%); mp. 82°C.

Example B3

a) Preparation of  (compound 3)

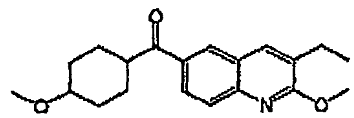
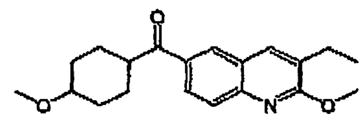
nBuLi 1.6M (0.07 mol) was added slowly at -70°C to a solution of intermediate (5) (0.058 mol) in THF (150ml). The mixture was stirred at -70°C for 30 minutes. A solution of 2,3-dihydro-1*H*-Indene-2-carbonitrile (0.07 mol) in THF (100ml) was added slowly. The mixture was stirred at -70°C for 1 hour, brought slowly to room temperature, hydrolized with H_2O and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (22g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ cyclohexane 80/20 to 100; 15-35μm). The pure fractions were collected and the solvent was evaporated. The second fraction was crystallized from 2-propanone/diethyl ether. The precipitate was filtered off and dried. Yield: 0.11g of compound (3). The filtrate was concentrated. Yield: 0.55g of compound (3); mp. 145°C.

b) Preparation of  and 

cis (compound 4) trans (compound 5)

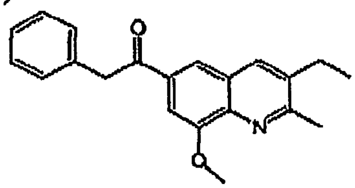
nBuLi 1.6M (0.022 mol) was added slowly at -70°C to a solution of intermediate (5) (0.018 mol) in THF (50ml). The mixture was stirred at -70°C for 1 hour, brought to -40°C, then cooled to -70°C. A solution of interm. 7 (0.018 mol) in THF (40ml) was added slowly. The mixture was stirred at -70°C for 1 hour, then brought to -20°C, hydrolyzed with H_2O and extracted with EtOAc. The organic layer was separated.

dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (6.5g) was purified by column chromatography over silica gel (eluent: toluene/EtOAc 90/10; 15-40μM). Two fractions (F1 and F2) were collected and the solvent was evaporated. F1 (2.4g) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 1.8g of compound (4) (29%); mp. 123°C. F2 (0.9g) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.2g of compound (5) (3%); mp. 120°C.

c) Preparation of  and 

CIS (compound 7) TRANS (compound 8)

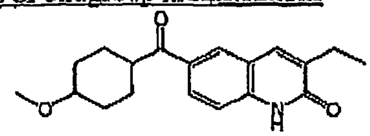
nBuLi 1.6M in exane (0.107 mol) was added dropwise at -78°C under N_2 flow to a mixture of intermediate (6) (0.089 mol) in THF. The mixture ws stirred at -78°C for 1 hour. A mixture of interm. 7 (150 ml) was added at -78°C under N_2 flow. The mixture was stirred at -78°C for 2 hours, brought to 0°C, poured out into H_2O and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (31g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15; 20-45 µm). Two pure fractions were collected and their solvents were evaporated. Yielding: 11 g of compound (7) (38%) and 8.2 g of compound (8) (28%).

d) Preparation of  (compound 503)

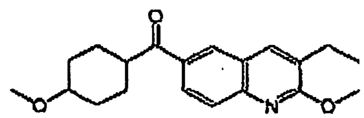
A solution of chloromethylbenzeen (0.0069 mol) in diethyl ether (8ml) was added slowly to a suspension of Mg (0.0069 mol) in a small amount of diethyl ether. The mixture was stirred at room temperature for 30 minutes (disparition of Mg), then cooled to 5°C. A solution of interm. 27 (0.0027 mol) in THF (8ml) was added slowly. The mixture was stirred at 5°C for 15 minutes, then at room temperature for 2 hours, poured out into H_2O and filtered over celite. The precipitate was washed with EtOAc. The filtrate was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (1g) was purified by column chromatography over kromasil (eluent: CH_2Cl_2 100 to CH_2Cl_2/CH_3OH 99/1; 15-40μm). The pure fractions were collected and the solvent was evaporated. The

residue (0.5g, 56%) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.14g of compound 503 (15%).

Example B4: examples of endgroup modifications

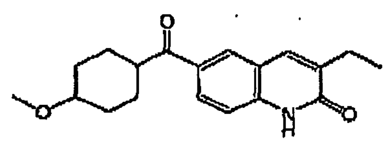
a) Preparation of  (compound 156)

trans

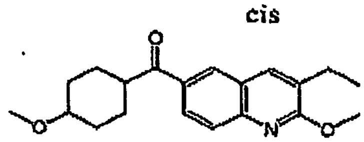
A mixture of  (compound 8)

trans

(prepared according to example B3.c) (0.018 mol) in HCl 3N (60ml) and THF (60ml) was stirred at 60°C overnight. The mixture was basified with a K_2CO_3 10% solution and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. Yield: 4.6g of compound (156) (82%).

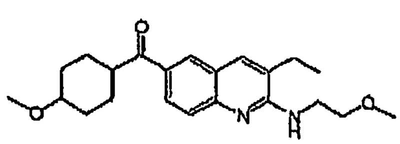
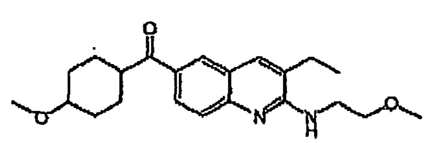
b) Preparation of  (compound 9)

cis

A mixture of  (compound 7)

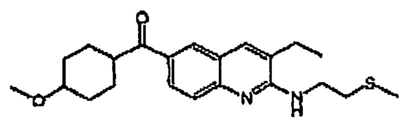
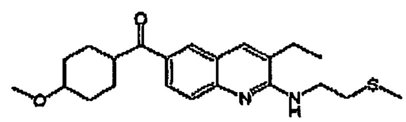
cis

(prepared according to example B3.c) (0.0122 mol) in HCl 3N (40ml) and THF (40ml) was stirred and refluxed overnight, poured out into water, basified with K_2CO_3 10% and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 40/60; 15-40μm). The pure fractions were collected and the solvent was evaporated. Yield: 2g of compound (9) (52%); mp. 226°C.

c) Preparation of  

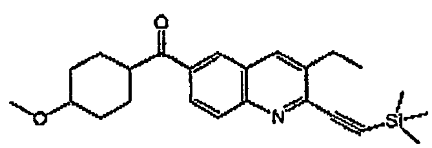
cis (compound 10) and (trans) (compound 11)

A mixture of compound (4) (0.0015 mol), 2-methoxyethanamine (0.003 mol) and K_2CO_3 (0.003 mol) in DMF (5ml) was stirred at 140°C for 48 hours. H_2O was added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 60/40; 15-40μm). Two fractions were collected and the solvent was evaporated. Both fractions were crystallized separately from pentane. The precipitate was filtered off and dried. Yield: 0.05g of compound (10) (9%; mp. 115°C) and 0.057g of compound (11) (10%; mp. 107°C).

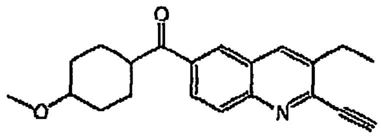
d) Preparation of  

cis (compound 12) and (trans) (compound 13)

A mixture of compound (4) (0.0015 mol) in 2-(methylthio)ethanamine (2ml) was stirred at 120°C for 8 hours. K_2CO_3 10% was added. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.2g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 70/30; 15-40μm). Two fractions were collected and the solvent was evaporated. The first fraction was crystallized from diethyl ether/petroleum ether. The precipitate was filtered off and dried. Yield: 0.08g of compound (12) (14%); mp. 120°C. The second fraction was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.18g of compound (13) (31%); mp. 125°C.

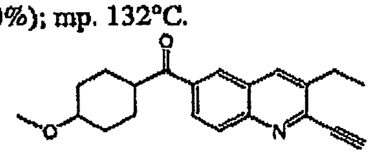
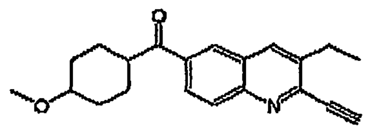
e) Preparation of  cis (compound 14)

A mixture of compound (4) (0.001507 mol), ethynyltrimethylsilane (0.003013 mol), CuI (0.000151 mol) and $Pd(PPh_3)_4$ (0.000151 mol) in *N,N*-diethylethanamine (5ml) was stirred at 100°C for 24 hours. Water was added. The mixture was filtered over celite, washed with EtOAc and the filtrate was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.3g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.3g) was crystallized from pentane. The precipitate was filtered off and dried. Yield: 0.11g of compound (14) (18%); mp. 114°C.

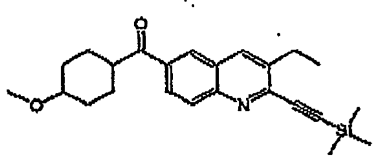
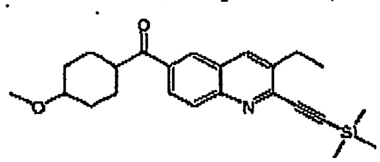
f) Preparation of  (compound 15)

cis

A mixture of compound (14) (0.013 mol) and KF (0.038 mol) in acetic acid (50ml) was stirred at room temperature for 2 hours. H_2O was added and the mixture was extracted with diethyl ether. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (4.4g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 70/30; 15-40μm). One fraction was collected and the solvent was evaporated. This fraction (3g, 73%) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 2.45g of compound (15) (60%); mp. 132°C.

g) Preparation of  

cis (compound 15) and trans (compound 17)

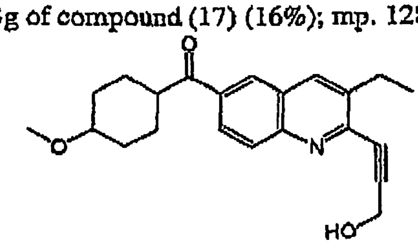
A mixture of  

cis (compound 14) and trans (compound 16)

prepared according to example B.7.a) (0.0056 mol) in KOH [1M, H_2O] (10ml) and methanol (30ml) was stirred at room temperature for 1 hour, poured out into water and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.2g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15 to 70/30; 15-40μm). Two fractions were collected and the solvent was evaporated.

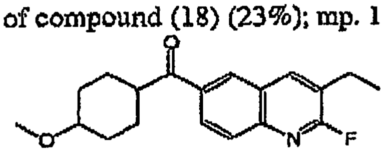
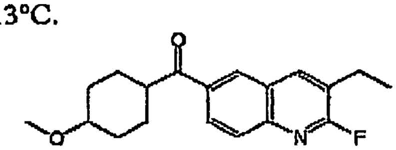
The first fraction was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.2g of compound (15) (11%); mp. 133°C.

The second fraction was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.3g of compound (17) (16%); mp. 128°C.

h) Preparation of  (compound 18)

cis

A mixture of compound (4) (0.001205 mol), 2-propyn-1-ol (0.002411 mol), $Pd(PPh_3)_4$ (0.000121 mol) and CuI (0.000121 mol) in *N,N*-diethylethanamine (5ml) was stirred at 100°C for 2 hours. Water was added. The mixture was filtered over celite, washed with EtOAc and extracted aith EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (0.7g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from petroleum ether and diethyl ether. The precipitate was filtered off and dried. Yield: 0.1g of compound (18) (23%); mp. 113°C.

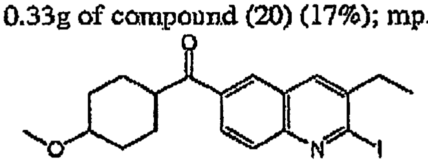
i) Preparation of  

cis (compound 19) and (trans) (compound 20)

A mixture of compound (4) (0.006027 mol) and KF (0.024108 mol) in DMSO (20ml) was stirred at 140°C. The solvent was evaporated till dryness. The residue was solidified in water and diethyl ether. The mixture was extracted with diethyl ether. The organic layer was separated, washed with diethyl ether, washed with a saturated solution of NaCl, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.7g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15; 15-40 μm). Three fractions were collected and their solvents were evaporated.

The first fraction was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.21g of compound (19) (11%); mp. 92°C.

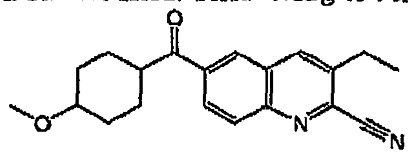
The second fraction was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.33g of compound (20) (17%); mp. 114°C.

j) Preparation of  (compound 21)

cis

A mixture of compound (4) (0.003013 mol), acetyl chloride (0.003315 mol) and sodium iodide (0.006027 mol) in CH_3CN (10ml) was stirred and refluxed for 1 hour. K_2CO_3 10% was added. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/20; 15-40 μm). Two fractions were collected and their solvents

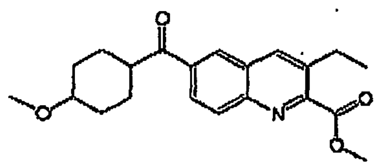
were evaporated. The first fraction was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.12g of compound (21); mp. 110°C.

k) Preparation of  (compound 22)

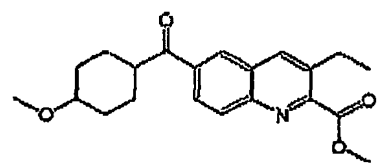
cis

A mixture of compound (21) (0.000898 mol), trimethylsilanecarbonitrile (0.001347 mol) and $Pd(PPh_3)_4$ (0.00009 mol) in *N,N*-diethylethanamine (5ml) was stirred at 100°C for 2 hours. Water was added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (0.4g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/20; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.18g, 62%) was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield : 0.13g of compound (22) (45%); mp. 138°C.

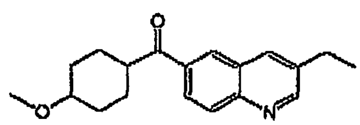
l) Preparation of



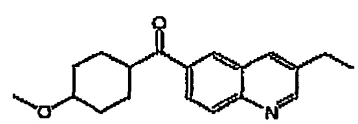
cis (compound 23)



(trans) (compound 24)



cis (compound 25)

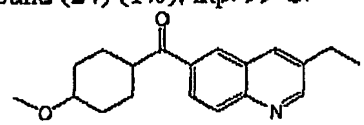


(trans) (compound 26)

A mixture of compound (4) (0.00603 mol), $Pd(OAc)_2$ (0.000603 mol), PPh_3 (0.00904 mol) and K_2CO_3 (0.012054 mol) in CO (gas) and methanol (40ml) was stirred at 90°C for 8 hours under a 5 bar pressure of CO. H_2O was added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (6g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 100/0 to 98/2; 15-35μm). Four fractions (F1-F4) were collected and the solvent was evaporated. Yield: 0.13g (cis) F1; 0.02g F2 (cis, compound 25); 0.055g F3 (trans, 3%) and 0.11g F4 (trans; compound 26).

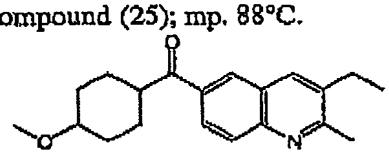
F1 was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.03g of compound (23) (1%); mp. 91°C.

F3 was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.035g of compound (24) (1%); mp. 99°C.

m) Preparation of  (compound 25)

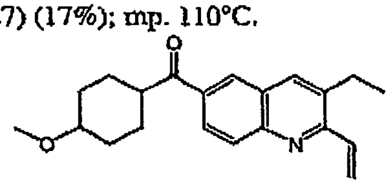
cis

A mixture of compound (4) (0.009 mol) and Zn (0.027 mol) in acetic acid (30ml) was stirred at 60°C for 4 hours, filtered over celite, washed with CH_2Cl_2, evaporated till dryness, solubilized in CH_2Cl_2 and washed with K_2CO_3 10%. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (4g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 75/25; 15-40μm). One fraction was collected and the solvent was evaporated. This fraction (1g 37%) was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: compound (25); mp. 88°C.

n) Preparation of  (compound 27)

cis

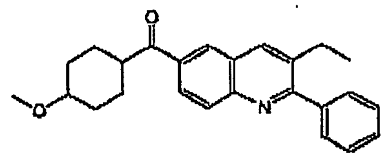
A mixture of compound (4) (0.001502 mol), $Sn(CH_3)_4$ (0.003004 mol) and $Pd(PPh_3)_4$ (0.00015 mol) in methylbenzene (5ml) was stirred and refluxed for 3 hours. K_2CO_3 10% was added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (0.7g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15; 15-40 μm). Two fractions (F1 and F2) were collected and their solvents were evaporated. Yield: 0.27g (F 1, starting material) and 0.14g (F2). F2 was crystallized from pentane and petroleum ether. The precipitate was filtered off and dried. Yield: 0.08g of compound (27) (17%); mp. 110°C.

o) Preparation of  (compound 28)

cis

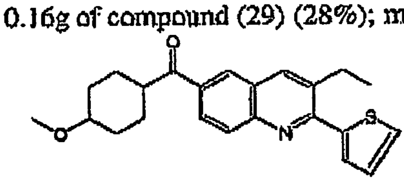
A mixture of compound (4) (0.001507 mol), tributylethenylstannane (0.002260 mol) and $Pd(PPh_3)_4$ (0.000151 mol) in dioxane (5ml) was stirred at 80°C for 8 hours. Water was added. The mixture was filtered over celite, washed with EtOAc and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (0.65g) was purified by column chromatography over

silica gel (eluent: cyclohexane/EtOAc 90/10; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.07g of compound (28) (14%); mp. 108°C.

p) Preparation of  (compound 29)

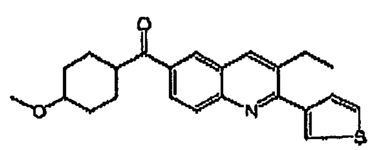
trans

A mixture of compound (5) (0.001507 mol), triphenyl(phenylmethyl)stannane (0.002260 mol) and $Pd(PPh_3)_4$ (0.000151 mol) in dioxane (5ml) was stirred at 80°C for 8 hours. Water was added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.4g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 96/4; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.38g) was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.16g of compound (29) (28%); mp. 112°C.

q) Preparation of  (compound 30)

cis

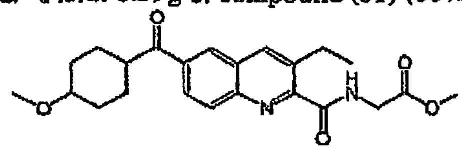
A mixture of compound (4) (0.001507 mol), tributyl-2-thienylstannane (0.00226 mol) and $Pd(PPh_3)_4$ (0.0001507 mol) in dioxane (5ml) was stirred at 80°C for 8 hours. K_2CO_3 10% was added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.7g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.65g) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.35g of compound (30) (61%); mp. 142°C.

r) Preparation of  (compound 31)

cis

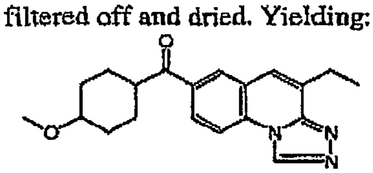
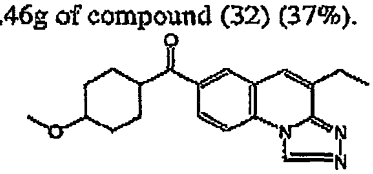
A mixture of compound (4) (0.0015 mol), 3-thienyl boronic acid (0.00226 mol), $Pd(PPh_3)_4$ (0.00015 mol) and dioxane was stirred and refluxed for 24 hours. K_2CO_3

10% was added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (0.8g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/20; 15-40μm). The pure fractions were collected and the solvent was evaporated. The residue (0.4g, 70%) was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.39g of compound (31) (68%); mp. 113°C.

s) Preparation of  (compound 32)

cis

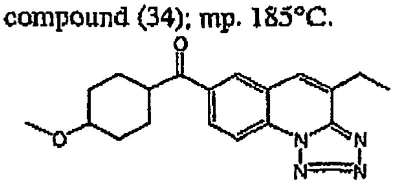
A mixture of compound (4) (0.003 mol), glycine methyl ester monohydrochloride (0.0066 mol) and $Pd(PPh)_4$ (0.0003 mol) in Et_3N (2ml) and toluene (10ml) was stirred at 100°C under 5 bar pressure of CO for 8 hours, filtered over celite, washed with CH_2Cl_2 and evaporated. The residue (2g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/20; 75-35μm). One fraction was collected and the solvent was evaporated. This fraction (1g 80%) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.46g of compound (32) (37%).

t) Preparation of  

cis (compound 33) (trans) (compound 34)

A mixture of compound (4) (0.003 mol) and hydrazinecarboxaldehyde (0.0045 mol) in 1-butanol (15ml) was stirred and refluxed overnight, poured out into water and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.1; 15-40 μm). Two fractions (F1 and F2) were collected and their solvents were evaporated. Yield: 0.3g F1 and 0.3g F2. F1 was crystallized from CH_3CN and diethyl ether. The precipitate was filtered off and dried. Yield: 0.102g of compound (33); mp. 224°C.

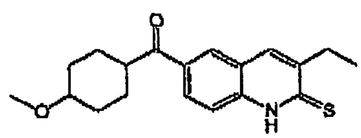
F2 was crystallized from CH_3CN and diethyl ether. The precipitate was filtered off and dried. Yield: 0.2g of compound (34); mp. 185°C.

u) Preparation of  (compound 35)

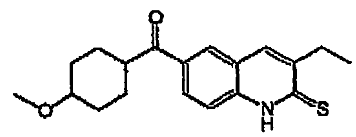
cis

A mixture of compound 4 (0.015 mol) and NaN_3 (0.045 mol) in DMF (50ml) was stirred at 140°C for 2 hours. K_2CO_3 10% was added and the mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (6g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 60/40; 15-40μm). The first fraction was collected and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 1.26g of compound (35) (24%); mp. 160°C.

v) Preparation of



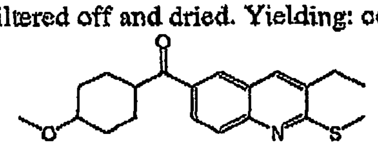
CIS
(compound 36)



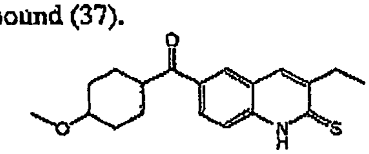
TRANS
(compound 37)

A mixture of compound (4) (0.009 mol) and thiourea (0.0099 mol) in ethyl alcohol (30ml) was stirred and refluxed for 12 hours and a solution of KOH (0.0149 mol) in H_2O (5ml) was added slowly. The mixture was stirred and refluxed for 1 hour, poured out into water and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (cyclohexane/EtOAc 70/30; 15-40μm). The pure fractions were collected and the solvent was evaporated. Yielding: 1.1g of F1 (37%) and 0.4g of F2 (13%). F1 was crystallized from 2-propanone. The precipitate was filtered off and dried. Yielding: compound (36). F2 was crystallized from 2-propanone. The precipitate was filtered off and dried. Yielding: compound (37).

w) Preparation of



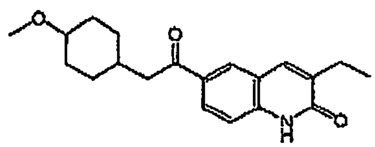
CIS
(compound 38)



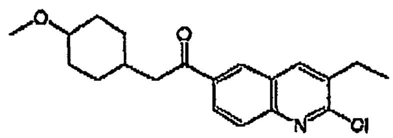
TRANS
(compound 39)

CH_3I (0.0034 mol) was added slowly at room temperature to a solution of compound (36) (0.0015 mol), compound (37) (0.0015 mol) and K_2CO_3 (0.0034 mol) in acetone (15ml). The mixture was stirred at room temperature for 8 hours. Water was added and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.2g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15; 15-40μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.6g F1 (57%), and 0.18g F2 (17%). F1 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.28g compound (38) (27%). F2 was crystallized from

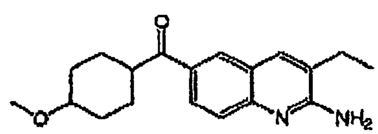
diethyl ether. The precipitate was filtered off and dried. Yielding: 0.065g of compound (39) (6%).

x) Preparation of  (compound 40)

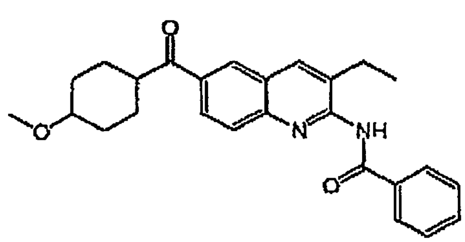
cis

A mixture of  compound (41) prepared

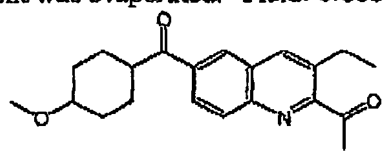
according to example B3.b (0.0014 mol) in HCl 3N (5ml) and THF (5ml) was stirred and refluxed for a weekend, then poured out into H_2O, basified with K_2CO_3 and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. Yielding: 0.5g of F. This fraction F was crystallized from 2-propanone. The precipitate was filtered off and dried. Yielding: 0.35g of compound (40) (74%).

y) Preparation of  (compound 188)

A mixture of compound (5) (0.045 mol), acetamide (0.90013 mol) and K_2CO_3 (0.225 mol) was stirred and refluxed at 200°C for 2 hours, cooled at room temperature, poured out into H_2O/CH_2Cl_2 ;and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (14.4 g) was crystallized from CH_3OH. The precipitate was filtered off and dried. The filtrate was evaporated. The residue (11.27g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 96/4/0.1; 15-35μm). The pure fractions were collected and the solvent was evaporated. Yielding: 4.2 g of compound (188) (65%).

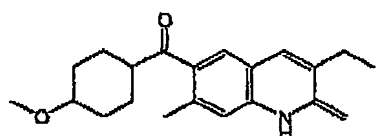
z) Preparation of  (compound 248)

A mixture of compound (188) (0.00032 mol), benzoic acid (1.5 equiv., 0.00048 mol), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide .HCl (1:1) (1.5 equiv., 0.00048 mol), N-hydroxybenzotriazole (1.5 equiv., 0.00048 mol) and Et_3N (1 equiv., 0.00032 mol) in CH_2CL_2 (2ml) was stirred at room temperature for 15 hours. The solvent was evaporated. The residue was purified by HPLC and the product fractions were collected and the solvent was evaporated. Yield: 0.066 g of compound (205) (49.50%).

aa) Preparation of  (compound 6)

trans

A mixture of interm. 20 (0.001507 mol) in HCl 3N (10ml) and THF (10ml) was stirred at room temperature for 8 hours, basified with K_2CO_3 10% and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.2g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.4g) was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.3g of compound (6) (58%); mp. 108°C.

ab) Preparation of  (compound 419)

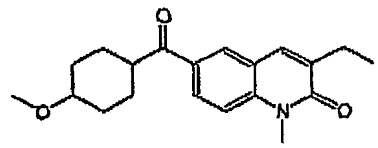
cis

A mixture of compound 213 (prepared according to B4) (0.00305 mol) and CH_3ONa (30% in CH_3OH) (0.00916 mol) in CH_3OH (25ml) was stirred and refluxed for 15 hours then cooled to room temperature, poured out into H_2O and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness. The residue (1.1g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc; 40/60; 15-40μm). Two fractions were collected and the solvent was evaporated. Yielding: 0.3g F1 and 0.5g F2 (50%) F2 was crystallized from diethyl ether/petroleum ether. The precipitate was filtered off and dried. Yielding: 0.26g F1 was crystallized from pentane. The precipitate was filtered off and dried. Yielding: 0.19g. This fraction was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH; 98/2; 15-40μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.11g. This fraction was purified by column chromatography over kromasil (eluent:CH_3OH/H_2O; 70/30). The pure

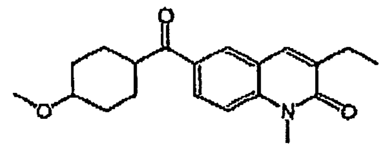
fractions were collected and the solvent was evaporated. Yielding: 0.09g. (9%) This fraction was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.08g of compound 419 (8%).

Example B5

Preparation of



cis (compound 42)

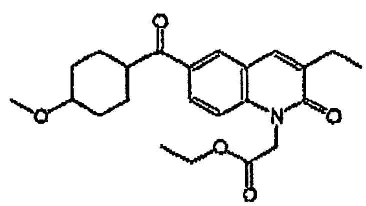


(trans) (compound 43)

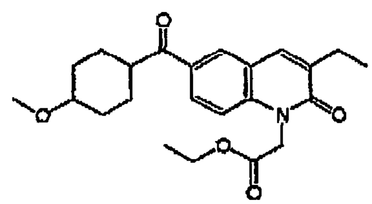
Iodomethane (0.00456 mol) was added at 5°C to a mixture of compound (9) (0.0019 mol), compound (8) (0.0019 mol) and tBuOK (0.00456 mol) in THF (30ml) under N_2 flow. The mixture was stirred at room temperature overnight, poured out into H_2O and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 65/35; 15-40μm). Two fractions were collected and the solvent was evaporated. Yield: 0.35g of compound (42) (30%; mp. 125°C) and 0.35g of compound (43) (30%; mp. 116°C).

Example B6

a) Preparation of

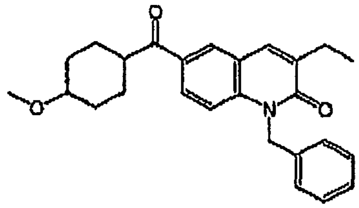
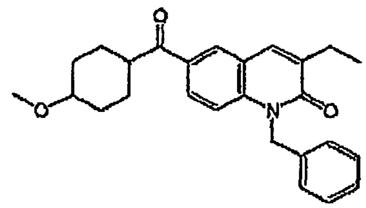


cis (compound 44)



(trans) (compound 45)

NaH 60% (0.01068 mol) was added at 0°C under N_2 flow to a mixture of compound (8) and compound (9) (0.0089 mol). The mixture was stirred for 30 minutes.
Ethyl bromoacetate (0.01068 mol) was added at 0°C. The mixture was stirred at room temperature for 1 hour, hydrolized with water and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 60/40; 15-40 μm). The desired fractions (F1-F4) were collected and the solvent was evaporated. Yield: 0.11g F1; 0.13g F2; 0.75g F3 and 0.8g F4.
F3 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: compound (44); mp. 152°C.
F4 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: compound (45); mp. 147°C.

b) Preparation of  

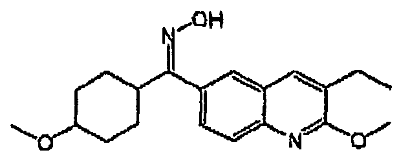
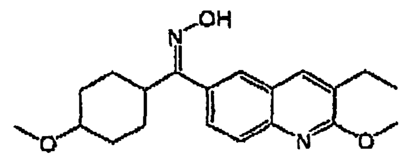
cis (compound 46) (trans) (compound 47)

Bromomethylbenzene (0.007 mol) was added dropwise at 0°C under N_2 flow to a solution of compound (8) and compound (9) (0.0064 mol) and NaH 60% (0.007 mol) in DMF (40ml). The mixture was stirred at room temperature for 1 hour, hydrolized with water and extracted with EtOAc. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 70/30; 15-40 μm). The desired fractions (F1-F4) were collected and the solvent was evaporated. Yield: 0.15g F1, 0.1g F2, 0.6g F3 (23%) and 0.8g F4.
F3 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.13g of compound (46); mp. 137°C.
F4 was crystallized from DIPE and petroleum ether. The precipitate was filtered off and dried. Yield: compound (47); mp. 130°C.

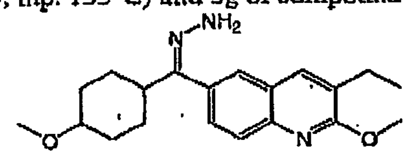
Example B7

a) 3-Chlorobenzenecarboperoxoic acid (0.088 mol) was added at 0°C to a solution of compound (48) (prepared according to example B2) (0.044 mol) in CH_2Cl_2 (200ml) and the mixture was stirred at room temperature for 12 hours. The mixture was washed with K_2CO_3 10%. The organic layer was dried ($MgSO_4$), filtered off and evaporated. The residue was recrystallized from $(C_2H_5)_2O$. Yield : 8.2g of cyclohexyl(3-methyl-6-quinolinyl)methanone,1-oxide (compound 49) (69%).
b) 4-Methyl benzenesulfonyl chloride (0.043 mol) was added to a solution of compound (49) (0.028 mol) in K_2CO_3 (400ml) and CH_2Cl_2 (400ml) and the mixture was stirred at room temperature for 1 hour. The mixture was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered off and evaporated. The residue was recrystallized from $(C_2H_5)_2O$. Yield : 6.64g of 6-(cyclohexylcarbonyl)-3-methyl-2(1H)-quinolinone (compound 50) (85%); mp. 256.1°C.

Example B8

a) Preparation of  [1α (A),4α] (compound 51)  [1α (B),4α] (compound 52)

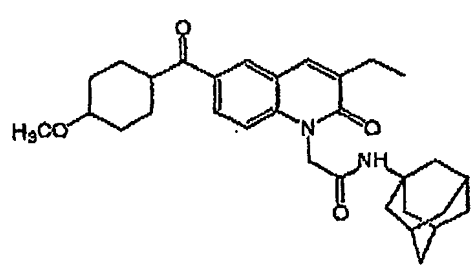
A mixture of compound (7) (0.0229 mol), hydroxylamine (0.0252 mol) and *N,N*-diethylethanamine (0.0252 mol) in ethanol (100ml) was stirred and refluxed for 6 hours, poured out into water and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was crystallized from CH_3CN. The precipitate was filtered off and dried. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 80/20; 15-40μm). Two fractions were collected and the solvent was evaporated. Yielding: 2.8g of compound (44) (36%; mp. 133°C) and 3g of compound (45) (38%; mp. 142°C).

b) Preparation of  (compound 53)

[1α(Z),4α]

Hydrazine (0.41 mol) was added at room temperature to a solution of compound (7) (0.015 mol) in ethanol (75ml). The mixture was stirred and refluxed for 1 night, poured out into water and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH/NH_4OH 98/2/0.1). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.8g of compound (53) (15%); mp. 110°C.

Example B9

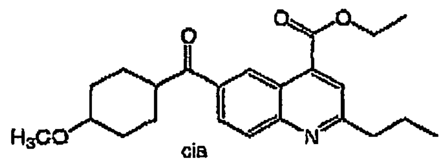
Preparation of  (compound 520)

Procedure for compounds 400, 401, 402, 403, 404 and 405. A mixture of interm. 21 (prepared according to A11) (0.000269 mol), amantadine hydrochloride (0.000404 mol; 1.5 eq.), *N'*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine

hydrochloride (0.000404 mol; 1.5 equiv.), 1-hydroxy-1*H*-benzotriazole (0.000404 mol; 1.5 equiv.) and Et_3N (0.000269 mol) in CH_2Cl_3 (2 ml) was stirred at room temperature for 12 hours. The solvent was evaporated. The residue was purified by HPLC. The product fractions were collected and the solvent was evaporated. Yield: 0.063 g of compound 520 (46.37%).

<u>Example B10</u>

Preparation of

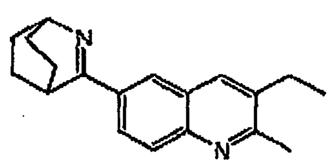


(compound 233)

A mixture of intermediate 27 (0.0026 mol) and intermediate 26 (0.0026 mol) in EtOH (380 ml) and H_2SO_4 conc. (19 ml) was stirred and refluxed for 15 hours, the cooled to room temperature, poured out into ice water, basified with K_2CO_3 and extracted with EtOAc. The organic layer was separated, dried (MgSO4), filtered, and the solvent was evaporated. The residue (17.9 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc; 80/20; 15-35μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.85 g of F1, 1.1 g F2 and 11.5 g of F3. F1 and F2 were crystallized separately from petroleum ether. The precipitate was filtered off and dried. Yielding: 0.34 g of compound 233.

<u>Example B11</u>

Preparation of

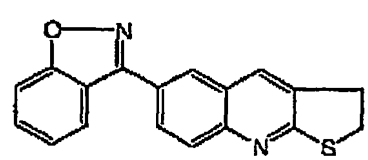


(compound 511)

A mixture of compound 22 (prepared according to B4) (0.004 mol) in HCl (3N) (20ml) and THF (20ml) was stirred and refluxed for 8 hours, poured out on ice, basified with NH_4OH and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (1.2g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$; 93/7/0.5; 15-40μm). Two fractions were collected and the solvent was evaporated. Yielding: 0.5g F1 (41%) and 0.4g of F2. F1 was crystallized from petroleum ether. The precipitate was filtered off and dried. Yielding: 0.17g of compound 511 (14%).

<u>Example B12</u>

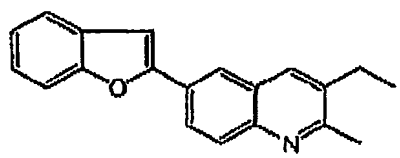
Preparation of



(compound 514)

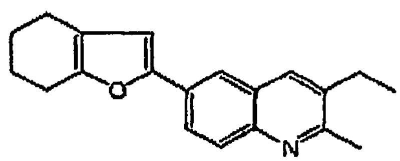
A mixture of compound 524 (prepared according to B9a) (0.0018 mol) and KOH 85% (0.0094 mol) in EtOH (15ml) was stirred and refluxed for 24 hours, poured out into H_2O and extracted with CH_2Cl_2. The organic layer was separated, dried (MgSO4), filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/Cyclohexane 80/20; 15-40μm). Two fractions were collected and the solvent was evaporated. Yielding: 0.35g F1 (64%) and 0.17g (SM) F1 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.33g of compound 514 (60%) (mp.:185°C).

Example B13

Preparation of  (compound 515)

A mixture of interm. 28 (0.019 mol), 2-benzofuranylboronic acid (0.028 mol), $Pd(PPh_3)_4$ (0.001 mol) and BHT (a few quantity) in dioxane (25ml) and Na_2CO_3 [2] (25ml) was stirred and refluxed for 8 hours and extracted with EtOAc. The aqueous layer was basified with NH_4OH and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (3.6g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1; 15-40μm). The pure fractions were collected and the solvent was evaporated. Yielding: 1.8g (33%). This fraction was crystallized from 2-propanone/diethyl ether. The precipitate was filtered off and dried. Yielding: 0.39g of compound 515 (7%) (mp.:134°C).

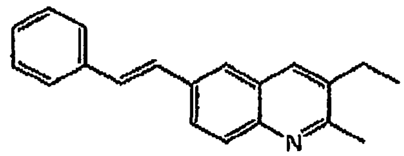
Example B14

Preparation of  (compound 526)

Triethylsilane (0.0012 mol) was added slowly at room temperature to a solution of interm. 32 (0.004 mol) in CF_3COOH (5ml) and AcOH (10ml). $NaBH_4$ (0.0012 mol) was added portionwise under N_2 flow. The mixture was stirred at room temperature for 8 hours, poured out on ice, basified with K_2CO_3 and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (1.2g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1; 15-40μm). Two fractions were collected and the solvent was evaporated. Yielding: 0.5g F1 (43%) and 0.4g F2. F1 was dissolved in iPrOH.

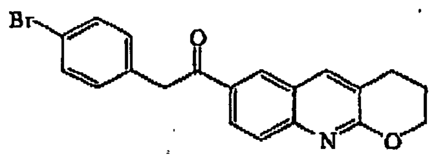
HCl/iPrOH (1 eq) were added. The precipitate was filtered off and dried; Yielding: 0.32g of compound 526 (mp.: 248°C).

Example B15

Preparation of  (compound 471)

A mixture of interm. 33 (0.082 mol) and 3-chloro-2-ethyl-2-butenal (0.098 mol) in AcOH (200ml) was stirred and refluxed for 8 hours. The solvent was evaporated till dryness. The residue was dissolved in CH_2Cl_2 and washed with K_2CO_3 10%. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (27g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 95/5 to 92/8; 15-35μm). Two fractions were collected and the solvent was evaporated. Yielding: 0.7g of F1 and 5.3g F2. F1 was crystallized from 2-propanone/diethyl ether. The precipitate was filtered off and dried. Yielding: 0.25g of compound 471 (2%) (mp.: 140°C).

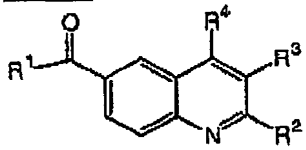
Example B16

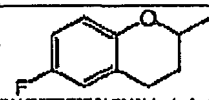
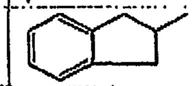
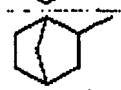
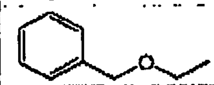
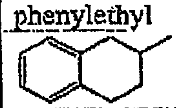
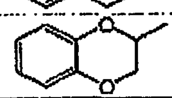
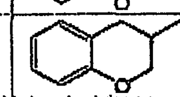
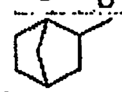
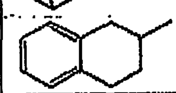
Preparation of  (compound 498)

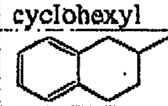
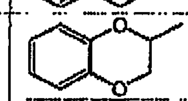
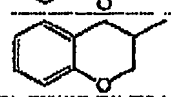
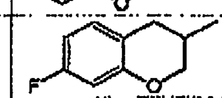
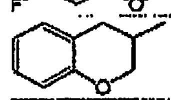
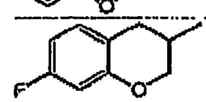
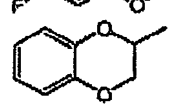
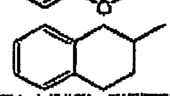
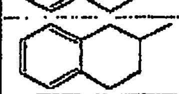
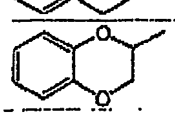
*n*BuLi (0.0417 mol) was added dropwise at -78°C to a solution of interm. 35 (prepared according to A17.b) (0.0379 mol) in THF (200ml) under N_2 flow. The mixture was stirred for 30 minutes. A solution of 4-bromo-*N*-methoxy-*N*-methylbenzeneacetamide (0.0568 mol) in THF (100ml) was added dropwise at -78°C. The mixture was stirred from -78°C to 0°C, poured out into H_2O and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated till dryness. The residue (20.9g) was purified by column chromatography over silica gel (eluent: toluene/EtOAc 60/40 to 50/50; 15-35μm). Two fractions were collected and the solvent was evaporated. Yielding: 4g of fraction 1 and 4g of fraction 2 (28%). Fraction 2 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 1g compound 528 (m.p. 195°C).

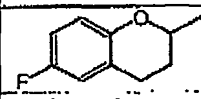
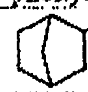
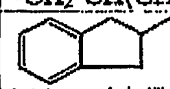
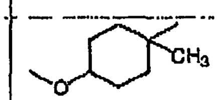
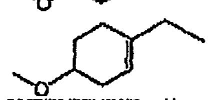
Tables 1 to 8 list the compounds of formula (I-A) and (I-B) which were prepared according to one of the above examples.

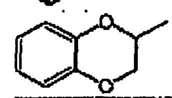
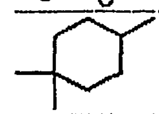
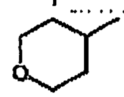
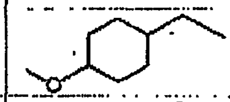
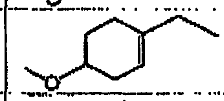
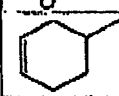
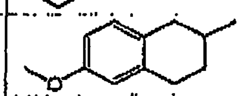
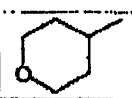
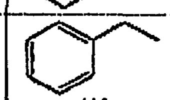
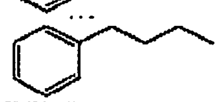
Table 1

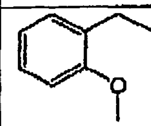
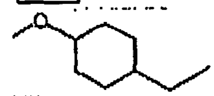
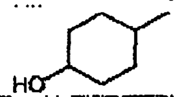
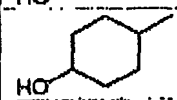
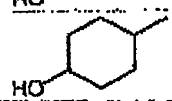
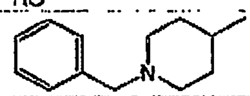
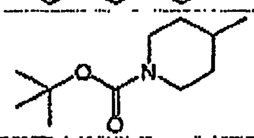
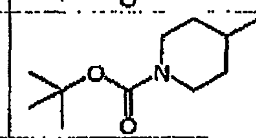
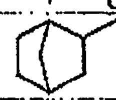
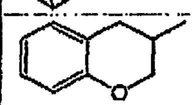
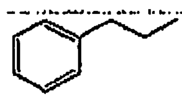
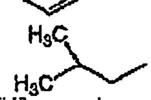
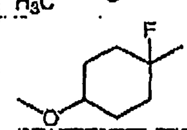


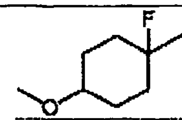
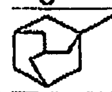
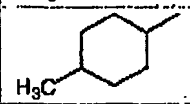
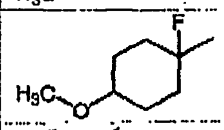
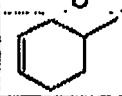
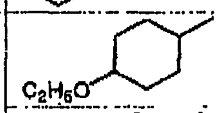
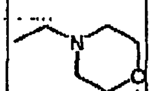
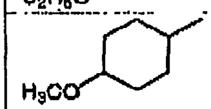
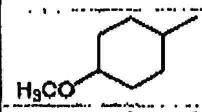
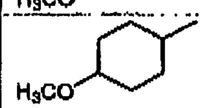
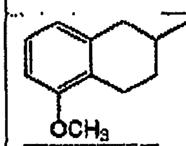
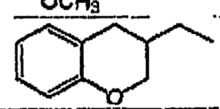
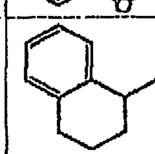
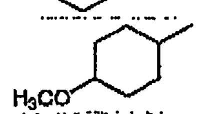
Co. no.	Ex. no.	R^2	R^3	R^4	R^1	physical data
54	B2	Cl	ethyl	H		-
3	B3a	Cl	ethyl	H		mp. 145°C
55	B3b	Cl	ethyl	H		mp. 131°C
56	B3b	Cl	ethyl	H		mp. 104°C
57	B3b	Cl	ethyl	H	phenylethyl	mp. 100°C
58	B3b	Cl	ethyl	H		mp. 126°C
59	B3b	Cl	ethyl	H		mp. 150°C
60	B3b	Cl	ethyl	H		mp. 138°C
61	B3b	OCH_3	ethyl	H		-
62	B3b	OCH_3	ethyl	H		mp. 130°C
63	B3b	OCH_3	ethyl	H		mp. 116°C
64	B3b	Cl	ethyl	H	$-(CH_2)_2-O-CH_3$	mp. 82°C
65	B3b	OCH_3	ethyl	H	1-methylcyclohexyl	mp. 82°C
66	B3b	OCH_3	ethyl	H	3-methoxycyclohexyl	trans; mp. 94°C

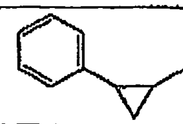
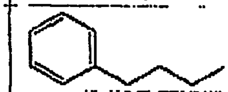
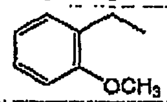
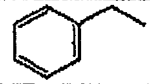
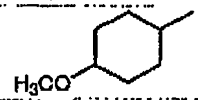
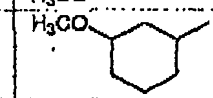
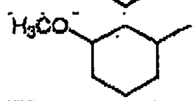
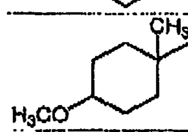
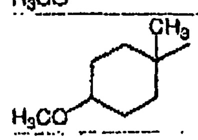
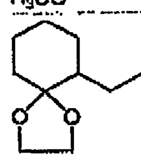
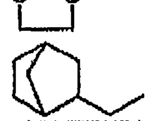
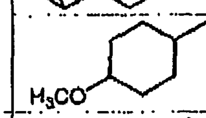
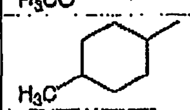
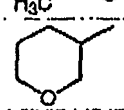
Co. no.	Ex. no.	R^2	R^3	R^4	R^1	physical data
67	B3b	OCH_3	ethyl	H	3-methoxycyclohexyl	cis; mp. 108°C
68	B3b	OCH_3	ethyl	H	4-(methylethoxy)-cyclohexyl	(A), mp. 82°C
69	B3b	OCH_3	ethyl	H	4-[$C(CH_3)_3$]cyclohexyl	cis; mp. 92°C
70	B3b	OCH_3	ethyl	H	4-[$C(CH_3)_3$]cyclohexyl	trans; mp. 108°C
71	B3b	OCH_3	ethyl	H	4-methylcyclohexyl	(B), mp. 92°C
72	B3b	OCH_3	ethyl	H	4-methylcyclohexyl	(A), mp. 80°C
2	B2	Cl	ethyl	H	CH_2-$CH(CH_3)_2$	mp. 82°C
73	B3b	Cl	ethyl	H	-CH_2-O-C_2H_5	mp. 82°C
48	B2	H	methyl	H	cyclohexyl	-
74	B4	I	ethyl	H		-
75	B4	I	ethyl	H		mp. 124°C
76	B4	I	ethyl	H		mp. 138°C
77	B4	I	ethyl	H		mp. 120°C
78	B4	CN	ethyl	H		mp. 128°C
79	B4	CN	ethyl	H		mp. 136°C
80	B4	CN	ethyl	H		mp. 120°C
81	B4	CN	ethyl	H		mp. 139°C
82	B4	methyl	ethyl	H		mp. 106°C
83	B4	methyl	ethyl	H		mp. 149°C

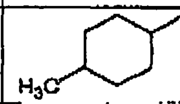
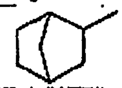
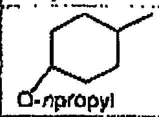
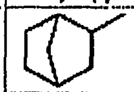
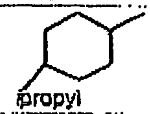
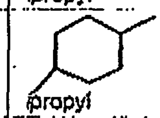
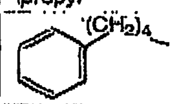
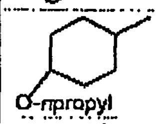
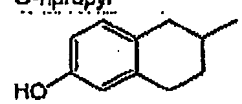
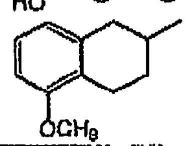
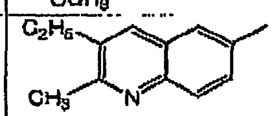
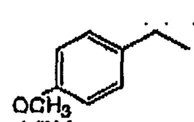
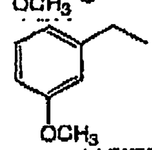
Co. no.	Ex. no.	R^2	R^3	R^4	R^1	physical data
84	B4	methyl	ethyl	H		mp. 118°C
85	B4	methyl	ethyl	H		mp. 180°C
86	B4	methyl	ethyl	H	phenylethyl	mp. 53°C
87	B4	methyl	ethyl	H		mp. 87°C
88	B4	methyl	ethyl	H	$-CH_2-CH(CH_3)_2$	mp. 68°C
89	B4	methyl	ethyl	H		mp. 120°C
31	B4	3-thiazolyl	ethyl	H	4-methoxycyclohexyl	cis; 113°C
90	B3b	OCH_3	H	H	4-methoxycyclohexyl	trans, mp. 126°C
91	B3b	OCH_3	H	H	4-methoxycyclohexyl	cis, mp. 100°C
92	B3b	OCH_3	H	CH_3	4-methoxycyclohexyl	cis; mp. 120°C
93	B3b	OCH_3	H	CH_3	4-methoxycyclohexyl	trans; mp. 111°C
94	B3b	OCH_3	methyl	H	4-methoxycyclohexyl	cis, mp. 96°C
95	B3b	OCH_3	phenyl	H	4-methoxycyclohexyl	cis; HCl (1:1), mp. 138°C
96	B3b	OCH_3	propyl	H	4-methoxycyclohexyl	trans; mp. 118°C
97	B3b	OCH_3	propyl	H	4-methoxycyclohexyl	cis; mp. 108°C
98	B3b	OCH_3	methyl	H	4-methoxycyclohexyl	cis; mp. 104°C
99	B4	$N(CH_3)_2$	ethyl	H		(B); mp. 102°C
100	B3b	Cl	ethyl	H		mp. 114°C
101	B4	methyl	ethyl	H	4-butoxycyclohexyl	cis; mp. 86°C

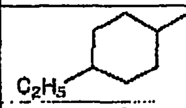
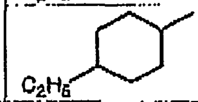
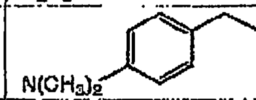
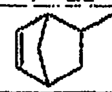
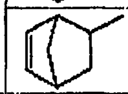
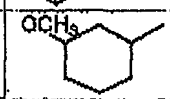
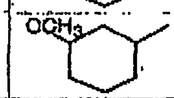
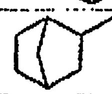
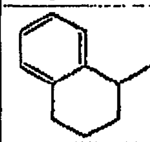
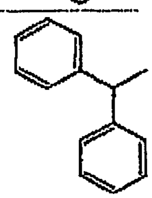
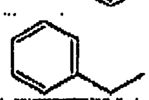
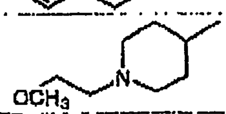
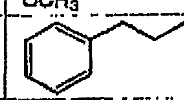
Co. no.	Ex. no.	R[2]	R[3]	R[4]	R[1]	physical data
102	B3b	Cl	ethyl	H		mp. 78°C
103	B3b	Cl	ethyl	H		mp. 91°C
104	B4	$N(CH_3)_2$	ethyl	H		mp. 103°C
105	B4	$N(CH_3)_2$	ethyl	H		mp. 170°C
106	B3b	Cl	ethyl	H		mp. 137°C
107	B3b	Cl	ethyl	H		mp. 137°C
108	B4	methyl	ethyl	ethyl	4-methoxycyclohexyl	cis; mp. 91°C
109	B4	methyl	ethyl	H	4-ethoxycyclohexyl	trans; mp. 150°C
110	B4	methyl	ethyl	H		mp. 90°C
111	B4	methyl	ethyl	H		mp. 94°C
112	B4	methyl	ethyl	H		mp. 176°C
113	B4	methyl	ethyl	H		mp. 106°C
114	B4	propyl	H	H	4-methoxycyclohexyl	cis; mp. 74°C
115	B4	methyl	ethyl	H	4-ethoxycyclohexyl	cis; mp. 108°C
116	B4	methyl	ethyl	H		mp. 110°C
117	B3b	Cl	ethyl	H		mp. 124°C
118	B3b	Cl	ethyl	H		mp. 107°C

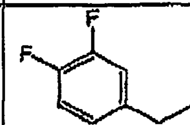
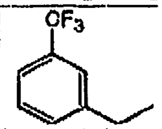
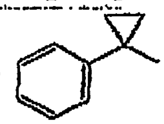
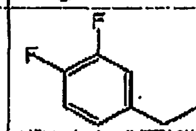
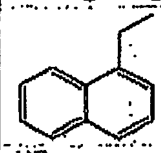
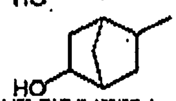
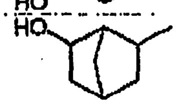
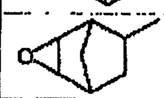
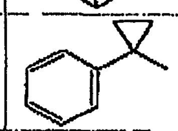
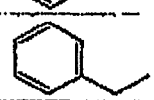
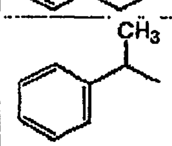
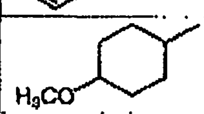
Co. no.	Ex. no.	R^2	R^3	R^4	R^1	physical data
119	B3b	Cl	ethyl	H		mp. 129°C
120	B4	methyl	ethyl	H		mp. 106°C
41	B3b	Cl	ethyl	H		trans; mp. 157°C
182	B3b	methyl	ethyl	H		cis; mp. 170°C
183	B3b	methyl	ethyl	H		trans; mp. 144°C
184	B3b	methyl	ethyl	H		mp. 138°C
185	B3b	Cl	ethyl	H		mp. 120°C
186	B3b	Cl	ethyl	H		
187	B3b	methyl	ethyl	H		mp. 162°C
216	B4	CC≡N	ethyl	H		mp.:160°C
217	B4	methyl	ethyl	H		.ethanedioate (1:1); mp.:143°C
218	B4	I	ethyl	H		mp.:102°C
219	B4	CC≡N	ethyl	H		mp.:115°C
220	B4	Cl	ethyl	H		(A); mp.:107°C

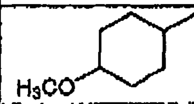
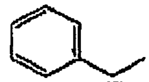
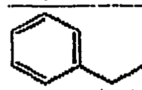
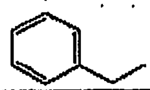
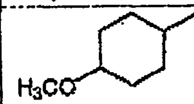
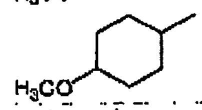
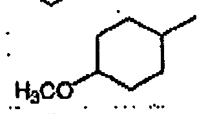
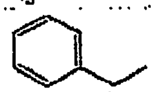
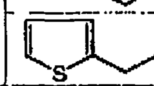
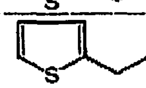
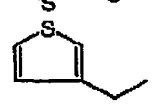
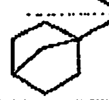
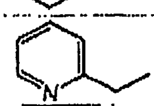
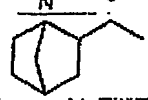
Co. no.	Ex. no.	R^2	R^3	R^4	R^1	physical data
221	B4	Cl	ethyl	H		(B); mp.:113°C
222	B4	I	ethyl	H		mp.:206°C
223	B4	Cl	ethyl	H		(trans); mp.:117°C
224	B4	methyl	ethyl	H		(A); mp.:103°C
225	B2	Cl	ethyl	H		mp.:94°C
226	B3b	Cl	ethyl	H		(trans); mp.:157°C
227	B3c	methoxy		H		mp.:204°C
228	B4	Cl	ethyl	H		(A); mp.:136°C
229	B3b	n-propyl	H	H		(trans);.HCl (1:1); mp.:150°C
230	B3b	Cl	ethyl	H		mp.:116°C
231	B3b	Cl	ethyl	H		mp.:120°C
232	B3b	Cl	ethyl	H		mp.:112°C
233	B10	*i*-propyl	H	C(=O)O-C_2H_5		(cis); mp.:91°C

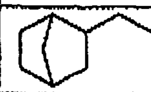
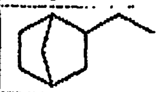
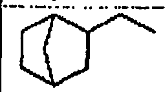
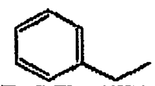
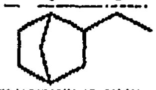
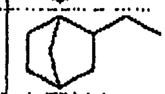
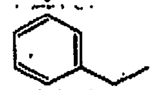
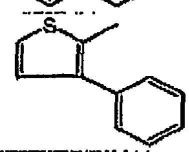
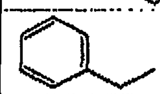
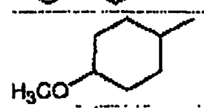
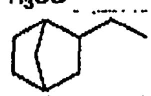
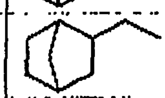
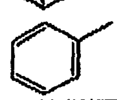
Co. no.	Ex. no.	R^2	R^3	R^4	R^1	physical data
234	B4	methyl	ethyl	H		mp.:122°C
235	B4	methyl	ethyl	H		mp.:106°C
236	B4	methyl	ethyl	H		mp.:104°C
237	B4	methyl	ethyl	H		mp.:90°C
238	B4	methyl	H	H		(cis); mp.:80°C
239	B3b	Cl	ethyl	H		(trans); mp.:126°C
240	B3b	Cl	ethyl	H		(cis); mp.:128°C
241	B4	methyl	ethyl	H		(A); mp.:90°C
242	B4	methyl	ethyl	H		(B); mp.:110°C
243	B3b	Cl	ethyl	H		mp.:134°C
244	B3b	Cl	ethyl	H		mp.:127°C
245	B4	NHC(=O)NH_2	ethyl	H		(cis); mp.:176°C
246	B4	methyl	ethyl	H		(B)
247	B3b	Cl	ethyl	H		mp.:92°C

Co. no.	Ex. no.	R^2	R^3	R^4	R^1	physical data
248	B4	methyl	ethyl	H		(A); mp.:80°C
249	B3b	Cl	ethyl	H		(B); mp.:138°C
250	B4	methyl	ethyl	H		(trans); mp.:118°C
251	B4	methyl	ethyl	H		(B);.HCl(1:1)
252	B3b	Cl	ethyl	H		(A)
253	B3b	Cl	ethyl	H		(B)
254	B3b	methyl	ethyl	H		mp.:74°C
255	B4	methyl	ethyl	H		(cis); mp.:68°C
256	B4	methyl	ethyl	H		mp.:210°C
257	B4	methyl	ethyl	H		mp.:113°C
258	B4	methyl	ethyl	H		mp.:92°C
259	B3b	methyl	ethyl	H		mp.:115°C
260	B3b	methyl	ethyl	H		mp.:60°C

Co. no.	Ex. no.	R^2	R^3	R^4	R^1	physical data
261	B3b	Cl	ethyl	H		(A); mp.:86°C
262	B3b	Cl	ethyl	H		(B); mp.:101°C
263	B3b	methyl	ethyl	H		mp.:130°C
264	B3b	Cl	ethyl	H		(A); mp.:124°C
265	B3b	Cl	ethyl	H		(B); mp.:126°C
266	B4	$N(CH_3)_2$	ethyl	H		(trans); mp.:102°C
267	B4	$N(CH_3)_2$	ethyl	H		(cis);.HCl(1:1); mp.:170°C
268	B4	methyl	ethyl	H		(A);.HCl(1:1); mp.:206°C
269	B4	methyl	ethyl	H		mp.:104°C
270	B3b	methyl	ethyl	H		mp.:117°C
271	B4	$NHC_2H_5OCH_3$	ethyl	H		-
272	B4	methyl	ethyl	H		-
273	B4	NH_2	ethyl	H		-

Co. no.	Ex. no.	R^2	R^3	R^4	R^1	physical data
274	B3b	Cl	ethyl	H		-
275	B3b	Cl	ethyl	H		mp.:99°C
276	B3b	Cl	ethyl	H		mp.:95°C
277	B4	methyl	ethyl	H		mp.:105°C
278	B3b	Cl	ethyl	H		mp.:141°C
279	B4	Cl	ethyl	H		mp.:168°C
280	B4	Cl	ethyl	H		-
281	B4	Cl	ethyl	H		mp.:140°C
282	B4	Cl	ethyl	H		mp.:169°C
283	B4	methyl	ethyl	H		mp.:96°C
284	B3b	Cl	$CH_2N(CH_3)_2$	H		mp.:115°C
285	B4	methyl	ethyl	H		mp.:133°C
286	B4	methyl	CH_2OCH_3	H		(trans); mp.:106°C

Co. no.	Ex. no.	R^2	R^3	R^4	R^1	physical data
287	B4	methyl	$CH_2N(CH_3)_2$	H		(cis); mp.:110°C
288	B3b	Cl	*n*-propyl	H		mp.:110°C
289	B4	NH_2	ethyl	H		mp.:218°C
290	B4	methyl	*n*-propyl	H		mp.:90°C
291	B3b	Cl	*n*-propyl	H		(cis); mp.:128°C
292	B3b	Cl	*n*-propyl	H		(trans); mp.:104°C
293	B3b	Cl	ethyl	H		mp.:106°C
294	B4	methyl	*n*-propyl	H		(cis); mp.:94°C
295	B4	methyl	$CH_2N(CH_3)_2$	H		mp.:83°C
296	B3b	Cl	ethyl	H		mp.:99°C
297	B3b	Cl	ethyl	H		mp.:110°C
298	B4	methyl	ethyl	H		mp.:93°C
299	B4	methyl	ethyl	H		mp.:105°C
300	B4	methyl	ethyl	H		mp.:114°C
301	B3b	methyl	ethyl	H		mp.:143°C
302	B4	methoxy	ethyl	H		mp.:93°C

Co. no.	Ex. no.	R^2	R^3	R^4	R^1	physical data
303	B4	methyl	ethyl	H		mp.:82°C
304	B4	n-butyl	ethyl	H		-
305	B3b	Cl	n-propyl	H		mp.:125°C
306	B1	methyl	$C(=O)OC_2H_5$	H		mp.:136°C
307	B4	methyl	n-propyl	H		mp.:81°C
308	B4	methoxy	n-propyl	H		mp.:80°C
309	B4	I	n-propyl	H		mp.:120°C
310	B3d	methyl	ethyl	H		.HCl(1:1); mp.:129°C
311	B3b	Cl	H	H		mp.:160°C
312	B3b	Cl	H	H		(trans); mp.:145°C
313	B3b	Cl	H	H		mp.:103°C
314	B4	n-propyl	n-propyl	H		.HCl(1:1); mp.:150°C
315	B4	n-propyl	ethyl	H		.HCl(1:1)
316	B4	n-propyl	H	H		.HCl(1:1); mp.:140°C
317	B3b	Cl	H	H		mp.:168°C

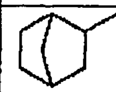
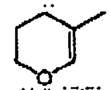
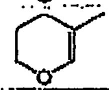
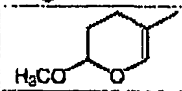
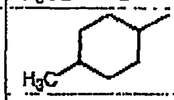
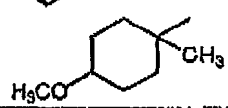
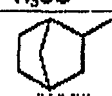
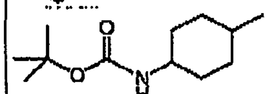
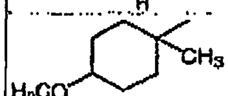
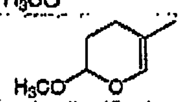
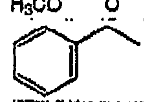
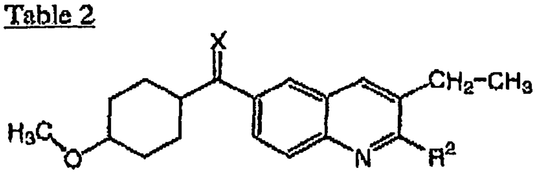
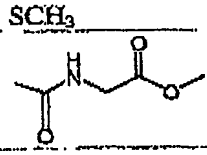
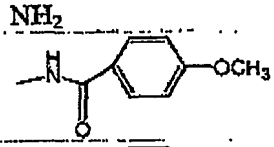
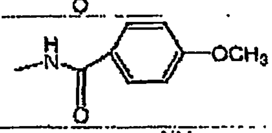
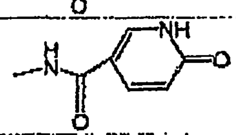
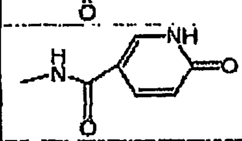
Co. no.	Ex. no.	R^2	R^3	R^4	R^1	physical data
318	B4	methyl	n-propyl	H		.HCl(1:1); mp.:200°C
509	B3b	Cl	ethyl	H		-
510	B4	methyl	ethyl	H		$.H_2O(1:1)$
513	B4	methyl	ethyl	H		-
516	B4	Cl	ethyl	H		mp.:120°C
517	B4	I	ethyl	H	$CH_2CH(CH_3)_2$	-
518	B4	Cl	ethyl	H		-
519	B4	Cl	ethyl	H		(A+B)
521	B4	I	ethyl	H		-
522	B4	methyl	ethyl	H		(A)
1	B4	methyl	ethyl	H		(A)
525	B4	Cl	ethyl	H		
527	B4	F	ethyl	H		mp.: 116°C

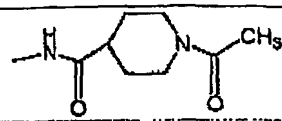
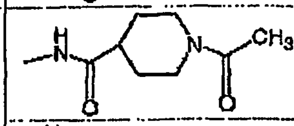
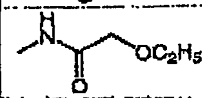
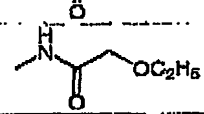
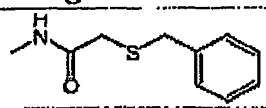
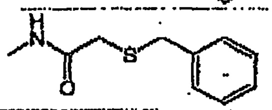
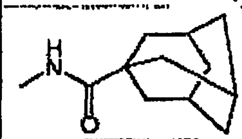
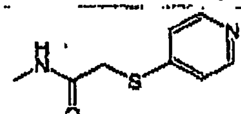
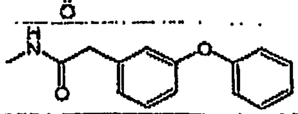
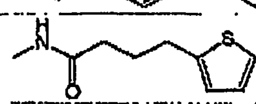
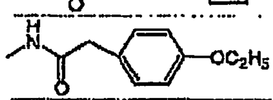
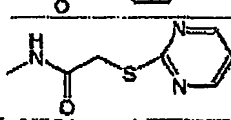
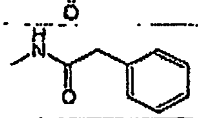
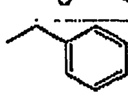
Table 2

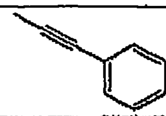
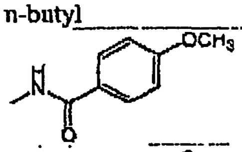
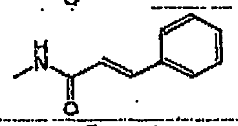
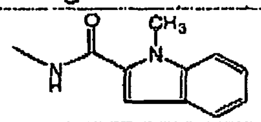
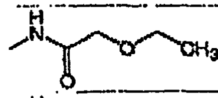
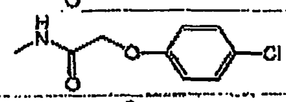
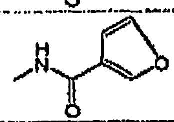
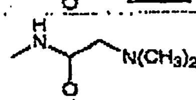
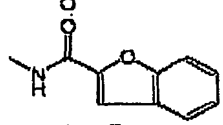
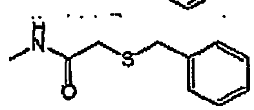
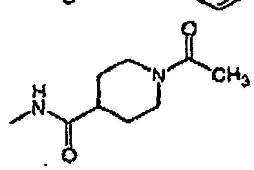


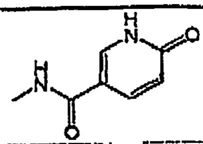
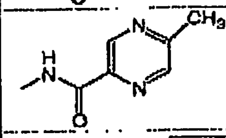
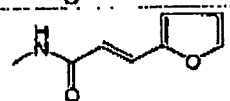
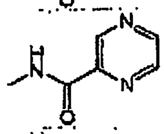
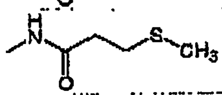
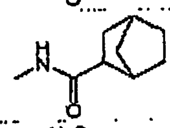
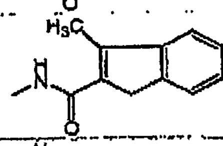
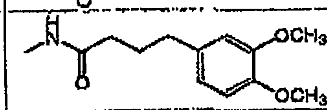
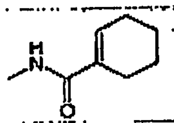
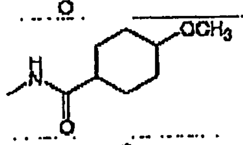
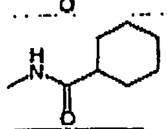
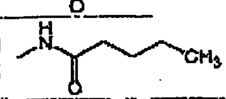
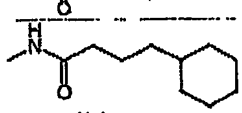
Co. no.	Ex. no.	R^2	X	physical data

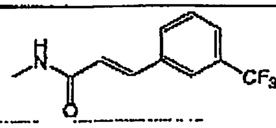
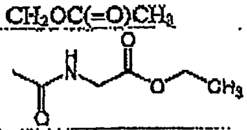
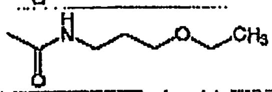
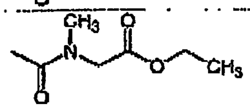
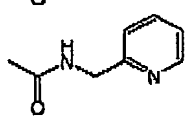
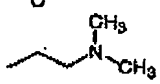
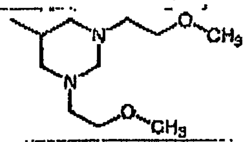
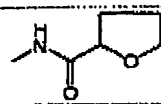
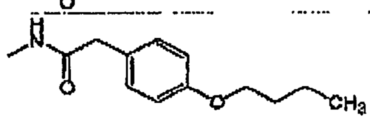
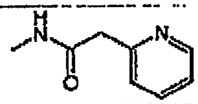
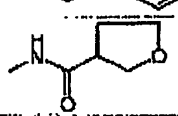
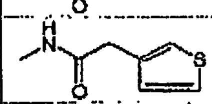
Co. no.	Ex. no.	R^2	X	physical data
5	B3b	Cl	O	trans; mp. 120°C
121	B3b	1-piperidinyl	O	cis; HCl (1:1)
122	B3b	1-piperidinyl	O	trans; HCl (1:1); mp. 128°C
123	B3b	4-thiomorpholinyl	O	cis; mp. 105°C
124	B3b	4-thiomorpholinyl	O	trans; mp. 115°C
125	B3b	4-morpholinyl	O	trans; mp. 118°C
126	B3b	4-morpholinyl	O	cis; mp. 118°C
127	B3b	$-N(CH_3)_2$	O	trans; mp. 96°C
128	B3b	$-N(CH_3)_2$	O	cis; mp. 114°C
4	B3b	Cl	O	cis; mp. 123°C
8	B3c	OCH_3	O	trans, mp. 68°C
7	B3c	OCH_3	O	cis, mp. 116°C
6	B4	acetyl	O	trans; mp. 108°C
129	B4	acetyl	O	cis; mp. 106°C
11	B4	$NH-(CH_2)_2-OCH_3$	O	trans; mp. 107°C
10	B4	$NH-(CH_2)_2-OCH_3$	O	cis; mp. 115°C
12	B4	$NH-(CH_2)_2-SCH_3$	O	cis; mp. 120°C
13	B4	$NH-(CH_2)_2-SCH_3$	O	trans; mp. 125°C
14	B4	$-C\equiv C-Si(CH_3)_3$	O	cis; mp. 114°C
16	B4	$-C\equiv C-Si(CH_3)_3$	O	trans; mp. 108°C
15	B4	$-C\equiv CH$	O	cis; mp. 132-133°C
17	B4	$-C\equiv CH$	O	trans; mp. 128°C
18	B4	$-C\equiv C-CH_2OH$	O	cis; mp. 113°C
130	B4	$-C\equiv C-CH_2OH$	O	trans; mp. 108°C
19	B4	F	O	cis; mp. 92-99°C
20	B4	F	O	trans; mp. 114°C
21	B4	I	O	cis; mp. 110°C
22	B4	CN	O	cis; mp. 137-138°C
26	B4	H	O	trans
23	B4	$-C(=O)-OCH_3$	O	cis; mp. 91°C
24	B4	$-C(=O)-OCH_3$	O	trans; mp. 99°C
25	B4	H	O	cis; mp. 88°C
27	B4	methyl	O	cis; mp. 110-112°C

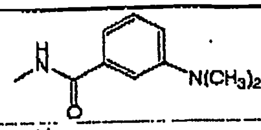
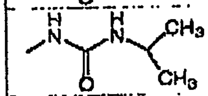
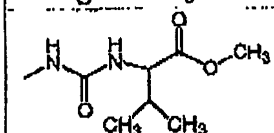
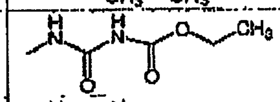
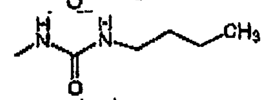
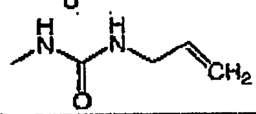
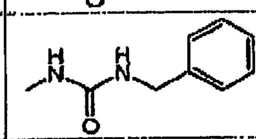
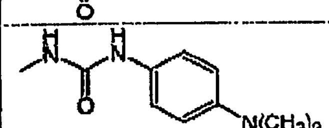
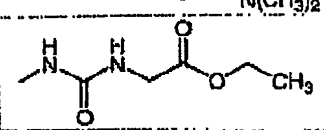
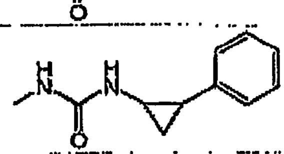
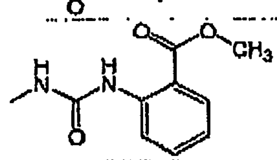
Co. no.	Ex. no.	R^2	X	physical data
131	B4	methyl	O	trans; mp. 25°C
28	B4	ethenyl	O	cis; mp. 108°C
132	B4	ethenyl	O	trans; mp. 103°C
29	B4	phenyl	O	trans; mp. 112°C
30	B4	2-thienyl	O	cis; 142°C
133	B4	2-thiazolyl	O	cis; 108°C
134	B4	2-furanyl	O	cis; mp. 105°C
51	B8a	OCH_3	N-OH	[1α(A),4α]; mp. 133°C
52	B8a	OCH_3	N-OH	[1α(B),4α]; mp. 142°C
53	B8b	OCH_3	NNH_2	[1α(Z),4α]; mp. 110°C
135	B4	NH_2	O	cis; mp. 203°C
136	B4	NH_2	O	trans; mp. 202°C
137	B4	$-C(=O)-OCH(CH_3)_2$	O	cis; mp. 105°C
138	B4	$-C(=O)-OCH(CH_3)_2$	O	trans; mp. 88°C
38	B4	SCH_3	O	cis; mp. 124°C
39	B4	SCH_3	O	trans; mp. 116°C
32	B4		O	cis; mp. 130°C
139	B4	ethyl	O	cis; mp. 180°C
188	B4	NH_2	O	cis + trans
189	B4		O	cis; mp. 154°C
190	B4		O	trans; mp. 156°C
191	B4		O	cis; mp. >260°C
192	B4		O	.H2O (1:1); trans; mp. 248°C

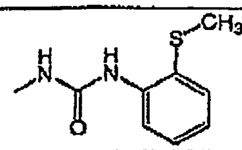
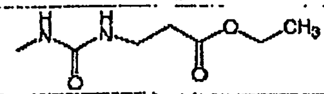
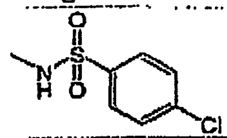
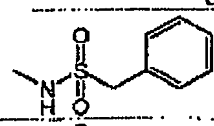
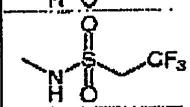
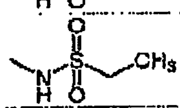
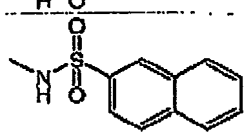
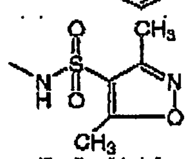
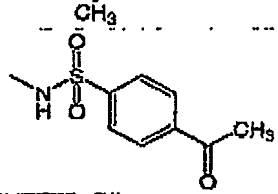
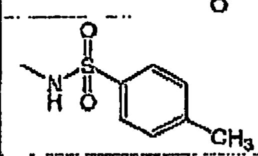
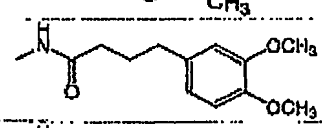
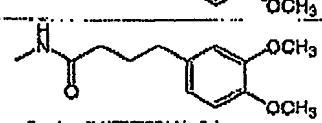
Co. no.	Ex. no.	R^2	X	physical data
193	B4		O	cis; mp. 224°C
194	B4		O	trans; mp. 234°C
195	B4		O	cis; mp. 108°C
196	B4		O	trans; mp. 127°C
197	B4		O	cis; mp. 150°C
198	B4		O	trans; mp. 90°C
199	B4		O	LC/MS $[M+H]^+$; 475.4
200	B4		O	LC/MS $[M+H]^+$; 464.3
201	B4		O	LC/MS $[M+H]^+$; 523.3
202	B4		O	LC/MS $[M+H]^+$; 465.3
203	B4		O	LC/MS $[M+H]^+$; 475.4
204	B4		O	LC/MS $[M+H]^+$; 465.3
205	B4		O	-
319	B4		O	(cis); ethanedioate(1:1); mp.:160°C

Co. no.	Ex. no.	R^2	X	physical data
320	B4		O	(cis); mp.:150°C
321	B4	methoxy	CH_2	(cis);.HCl(1:1); mp.:118°C
322	B4	n-butyl	O	(cis);.HCl(1:1); mp.:158°C
323	B4		O	-
324	B4		O	-
325	B4		O	-
326	B4		O	-
327	B4		O	-
328	B4		O	-
329	B4		O	-
330	B4		O	-
331	B4		O	-
332	B4		O	-
333	B4		O	-

Co. no.	Ex. no.	R^2	X	physical data
334	B4		O	-
335	B4		O	-
336	B4		O	-
337	B4		O	-
338	B4		O	-
339	B4		O	-
340	B4		O	-
341	B4		O	-
342	B4		O	-
343	B4		O	-
344	B4		O	-
345	B4		O	-
346	B4		O	-

Co. no.	Ex. no.	R^2	X	physical data
347	B4		O	-
348	B4	$CH_2OC(=O)CH_3$	O	(cis); mp.:74°C
349	B4		O	-
350	B4		O	-
351	B4		O	-
352	B4		O	-
353	B4		O	(A);.HCl(1:2).H2O(1:1); mp.:166°C
354	B4		O	(cis)
355	B4		O	-
356	B4		O	-
357	B4		O	-
358	B4		O	-
359	B4		O	-
360	B4		O	-

Co. no.	Ex. no.	R^2	X	physical data
361	B4		O	-
362	B4		O	-
363	B4		O	-
364	B4		O	-
365	B4		O	-
366	B4		O	-
367	B4		O	-
368	B4		O	-
369	B4		O	-
370	B4		O	-
371	B4		O	-
372	B4		O	-

Co. no.	Ex. no.	R^2	X	physical data
373	B4		O	-
374	B4		O	-
375	B4		O	-
376	B4		O	-
377	B4		O	-
378	B4		O	-
379	B4		O	-
380	B4		O	-
381	B4		O	-
382	B4		O	-
383	B4		O	(cis); mp.:148°C
384	B4		O	(trans); mp.:141°C

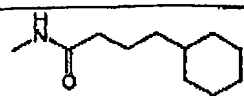
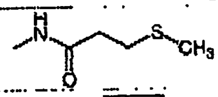
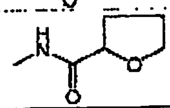
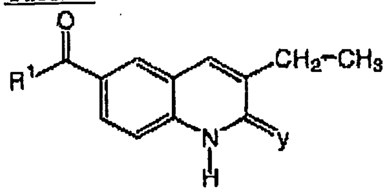
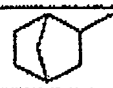
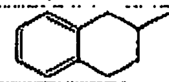
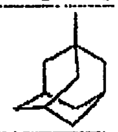
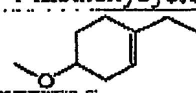
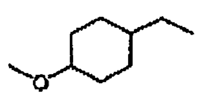
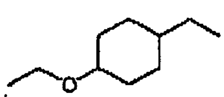
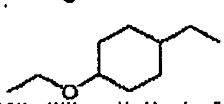
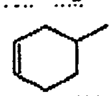
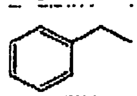
Co. no.	Ex. no.	R^2	X	physical data
385	B4		O	mp.:130°C
386	B4		O	(cis); mp.:140°C
387	B4		O	(trans); mp.:155°C

Table 3



Co. no.	Ex. no.	Y.	R^1	physical data
140	B4	O		mp. 220°C
141	B4	O		mp. 213°C
142	B4	O		mp. 148°C
143	B4	O	1-methylcyclohexyl	mp. 195-210°C
144	B4	O	3-methoxycyclohexyl	cis; mp. 156°C
145	B4	O	3-methoxycyclohexyl	trans; mp. 156-163°C
146	B4	O	4-(dimethylethyl)cyclohexyl	mp. 230°C
147	B4	O	4-(methylethoxy)cyclohexyl	mp. 186°C
148	B4	O	4-methylcyclohexyl	trans; mp. 214°C
36	B4	S	4-methoxycyclohexyl	cis; mp. 224°C
37	B4	S	4-methoxycyclohexyl	trans; mp. 220°C
149	B4	O		mp. 188°C
40	B4	O		mp. 192°C
150	B4	O		cis; mp. 226°C
151	B4	O		trans; mp. 226°C
152	B4	O		mp. 213°C
153	B4	O		mp. 200°C

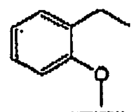
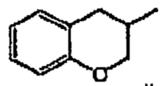
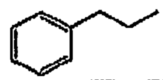
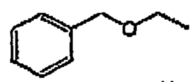
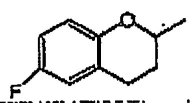
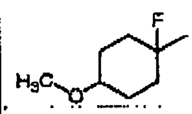
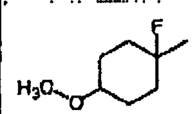
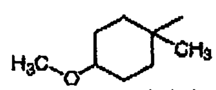
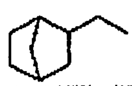
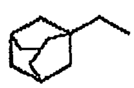
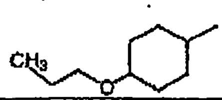
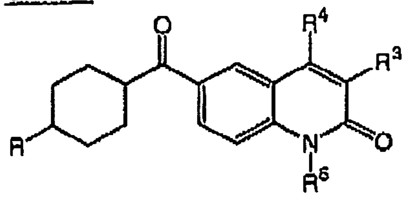
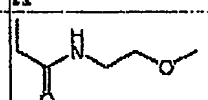
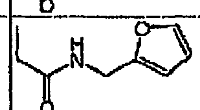
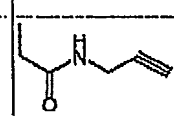
Co. no.	Ex. no.	Y.	R^1	physical data
154	B4	O		mp. 210°C
155	B4	O	4,4-dimethylcyclohexyl	mp. 242°C
388	B4	O	$CH_2CH(CH_3)_2$	mp. 189°C
389	B4	O		mp. 228°C
390	B4	O		mp. 197°C
391	B4	O		mp. 145°C
392	B4	O		mp. 192°C
393	B4	O		(B); mp.:224°C
394	B4	O		(A); mp.:201°C
395	B4	O		(A); mp.:207°C
396	B4	O		mp.:212°C
397	B4	O		(B); mp.:238°C
398	B4	O		mp.:234°C
399	B4	O		(cis); mp.:192°C

Table 4



Co. no.	Ex. o.	R^3	R^4	R^5	R	physical data
156	B4	ethyl	H	H	OCH_3	trans; mp. 252°C
157	B4	H	H	H	OCH_3	(cis + trans); mp. 244°C
158	B4	H	methyl	H	OCH_3	cis; mp. >260°C
159	B4	methyl	H	H	OCH_3	cis; mp. 254°C
160	B4	methyl	H	H	OCH_3	trans; mp. >260°C
161	B4	propyl	H	H	OCH_3	mp. 208°C
162	B4	propyl	H	H	OCH_3	trans; mp. 232°C
9	B4	ethyl	H	H	OCH_3	cis; mp. 224-226°C
43	B5	ethyl	H	CH_3	OCH_3	trans; mp. 116°C
42	B5	ethyl	H	CH_3	OCH_3	cis; mp. 125°C
44	B6	ethyl	H	CH_2-$COOC_2$H5	OCH_3	cis; mp. 152°C
45	B4	ethyl	H	CH_2-$COOC_2$H5	OCH_3	trans; mp. 147°C
46	B4	ethyl	H	benzyl	OCH_3	cis; mp. 137°C
47	B4	ethyl	H	benzyl	OCH_3	trans; mp. 130°C
50	B7	methyl	H	H	H	mp. 256.1°C
163	B4	ethyl	ethyl	H	OCH_3	cis; mp. 221°C
164	B4	ethyl	ethyl	H	OCH_3	cis; mp. 221°C
165	B4	ethyl	ethyl	H	OCH_3	trans; mp. 215°C
166	B4	ethyl	H		OCH_3	LC/MS $[M+H]^+$; 429.4
167	B4	ethyl	H		OCH_3	LC/MS $[M+H]^+$; 451.3
168	B4	H	H	H	OCH_3	cis; mp. 106°C
169	B4	ethyl	H		OCH_3	LC/MS $[M+H]^+$; 409.3

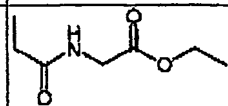
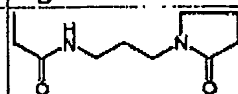
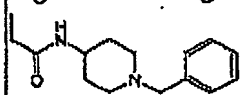
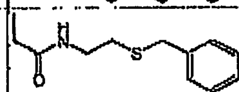
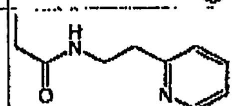
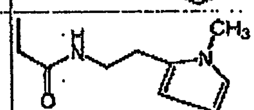
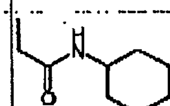
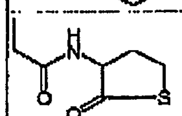
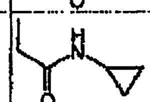
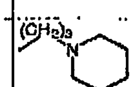
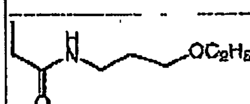
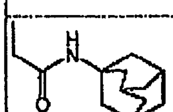
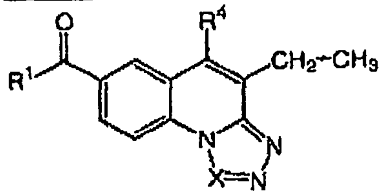
Co. no.	Ex. .o.	R^3	R^4	R^5	R	physical data
400	B9	ethyl	H		OCH_3	-
401	B9	ethyl	H		OCH_3	-
402	B9	ethyl	H		OCH_3	-
403	B9	ethyl	H		OCH_3	-
404	B9	ethyl	H		OCH_3	-
405	B9	ethyl	H		OCH_3	-
406	B4	ethyl	H		OCH_3	-
407	B4	ethyl	H		OCH_3	-
408	B4	ethyl	H		OCH_3	-
409	B3b		H	H	OCH_3	mp.:168°C
410	B4	CH_2OCH_3	H	H	OCH_3	mp.:194°C
508	B4	ethyl	H		OCH_3	-
520	B9	ethyl	H		OCH_3	-

Table 5



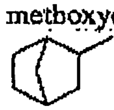
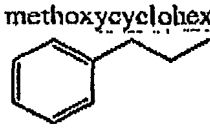
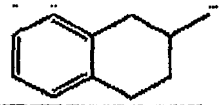
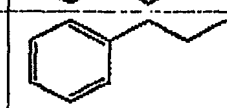
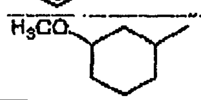
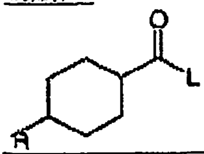
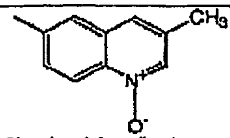
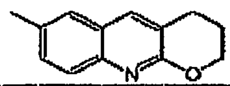
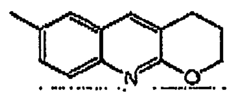
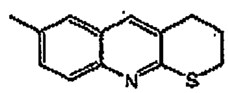
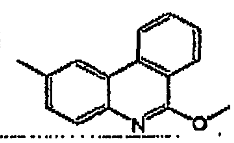
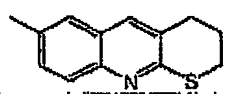
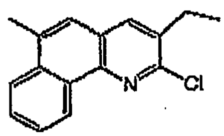
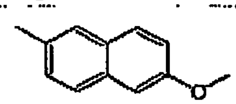
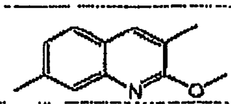
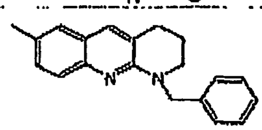
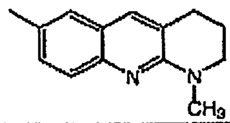
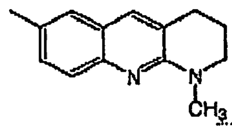
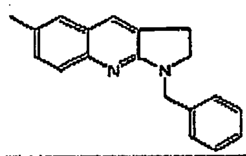
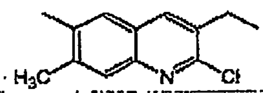
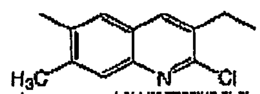
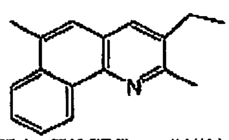
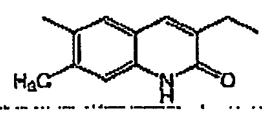
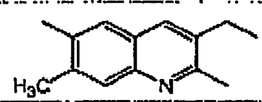
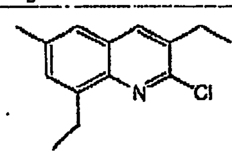
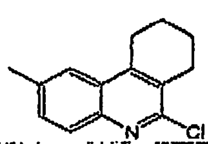
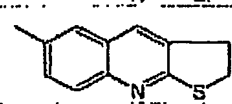
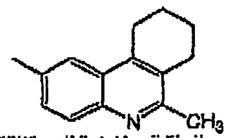
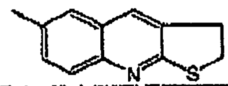
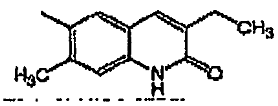
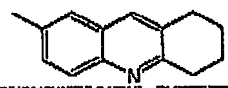
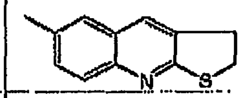
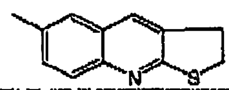
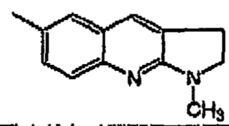
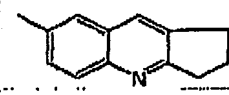
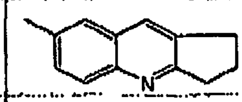
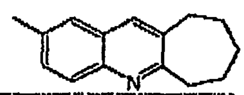
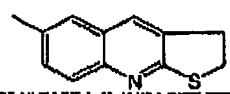
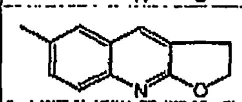
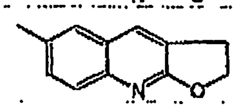
Co. no.	Ex. no.	R^4	R^1	X	physical data
33	B4	H	methoxycyclohexyl	CH	cis; mp. 224°C
34	B4	H	methoxycyclohexyl	CH	trans; mp. 185°C
35	B4	H	methoxycyclohexyl	N	cis; mp. 160-172°C
170	B4	H	methoxycyclohexyl	N	trans; mp. 146°C
171	B4	H		N	(B); mp. 165°C
172	B4	H	methylcyclohexyl	N	cis+trans; mp. 143°C
173	B4	ethyl	methoxycyclohexyl	N	cis; mp.:126°C
411	B4	H		N	mp.:109°C
412	B4	H		N	mp.:180°C
413	B4	H		N	(A)
414	B4	H		N	mp.:156°C

Table 6



Co. no.	Ex. no.	R	L	physical data
49	B7	H		-
174	B3b	OCH_3		cis; mp.115°C
175	B3b	OCH_3		trans; mp.141°C
176	B3b	OCH_3		cis; mp.149°C
177	B3b	OCH_3		mp.126°C
178	B3b	OCH_3		trans; mp.160°C
179	B3b	OCH_3		cis; mp.119°C
180	B3b	OCH_3		trans; mp.124°C
181	B3b	OCH_3		trans; mp.92°C
206	B3b	OCH_3		cis; m.p. 144°C

Co. no.	Ex. no.	R	L	physical data
207	B3b	OCH_3		trans; m.p. 125°C
208	B3b	OCH_3		cis; m.p. 127°C
209	B3b	OCH_3		cis; m.p. 101°C
210	B3b	OCH_3		cis; m.p. 104°C
211	B3b	OCH_3		trans; m.p. 134°C
212	B4	OCH_3		cis; m.p. 141°C
213	B4	OCH_3		trans; m.p. 215°C
214	B4	OCH_3		cis; m.p. 139°C
215	B3b	OCH_3		trans
415	B3b	OCH_3		(cis); mp.:136°C
416	B3b	OCH_3		(cis)

Co. no.	Ex. no.	R	L	physical data
417	B4	OCH_3		(cis); mp.:149°C
418	B3b	OCH_3		(trans); mp.:132°C
419	B4	OCH_3		(cis); mp.:217°C
420	B3b	OCH_3		(cis); .HCl(1:1); mp.:200°C
421	B4	OH		(cis); mp.:215°C
422	B4	OH		(trans); mp.:178°C
423	B3b	OCH_3		mp.:160°C
424	B3b	OCH_3		(cis); mp.:106°C
425	B3b	OCH_3		(trans); mp.:120°C
426	B3b	OCH_3		(cis); mp.:121°C
427	B3b	H		mp.:156°C
428	B3b	OCH_3		(cis); mp.:156°C
429	B3b	OCH_3		(trans); mp.:197°C

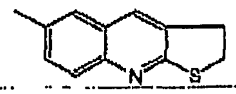
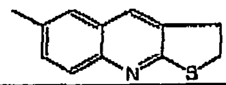
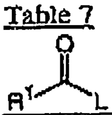
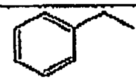
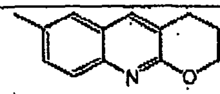
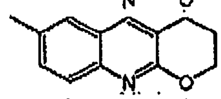
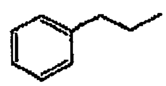
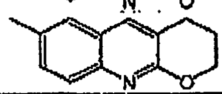
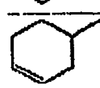
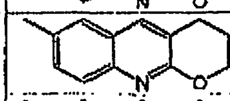
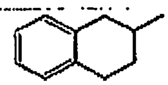
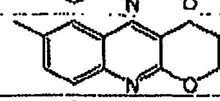
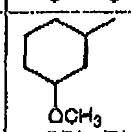
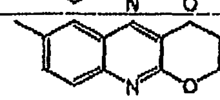
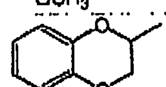
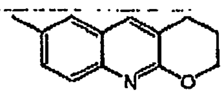
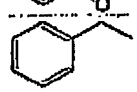
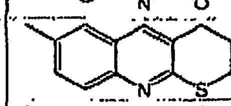
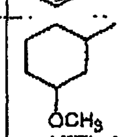
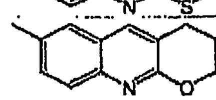
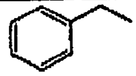
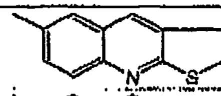
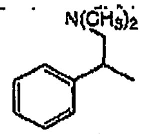
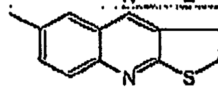
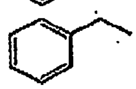
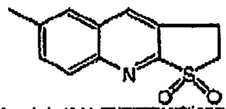
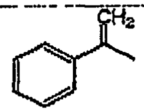
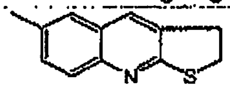
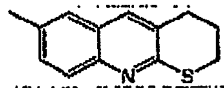
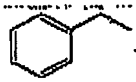
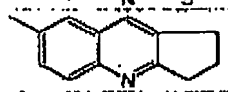
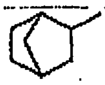
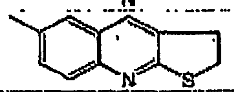
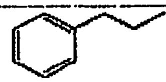
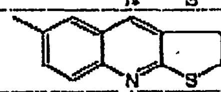
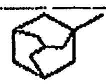
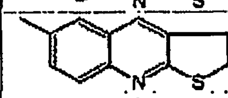
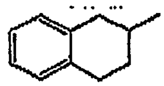
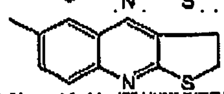
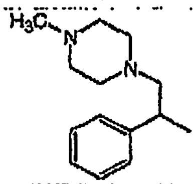
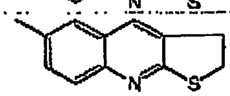
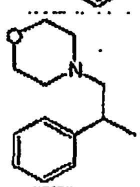
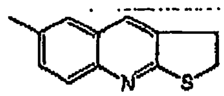
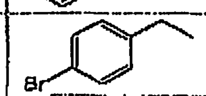
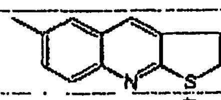
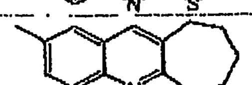
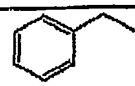
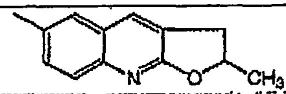
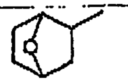
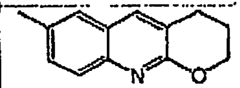
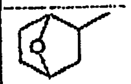
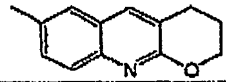
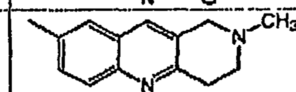
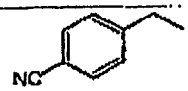
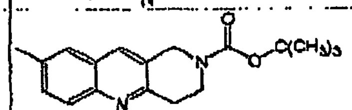
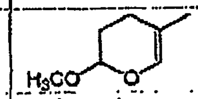
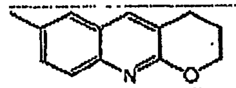
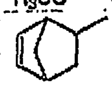
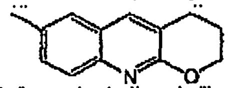
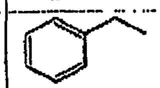
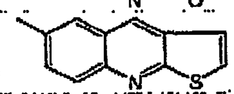
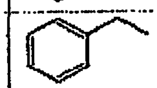
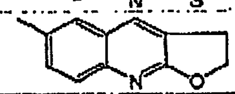
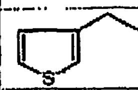
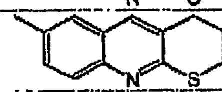
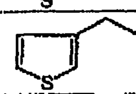
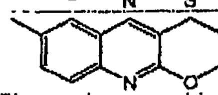
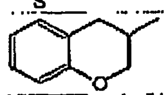
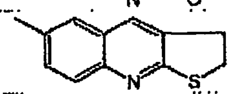
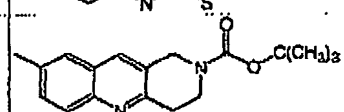
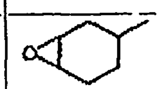
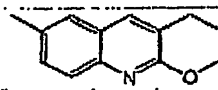
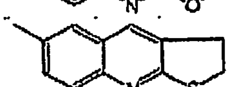
Co. no.	Ex. no.	R	L	physical data
430	B3b	CH_3		(B)
431	B3b	CH_3		(A)

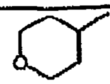
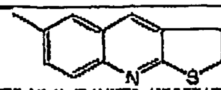
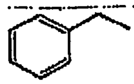
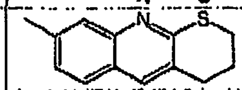
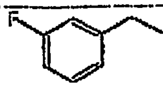
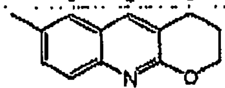
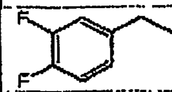
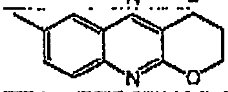
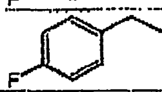
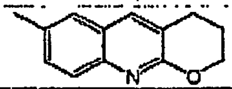
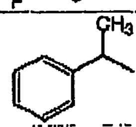
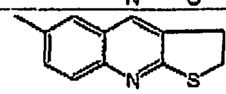
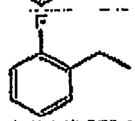
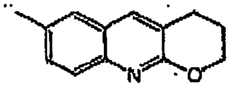
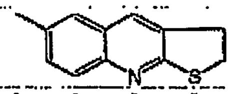
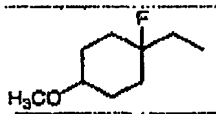
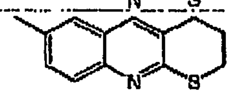
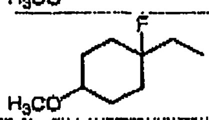
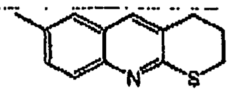
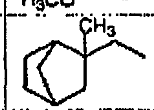
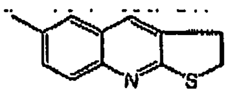
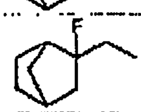
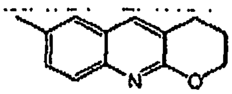
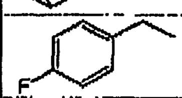
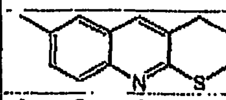
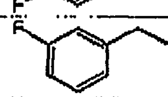
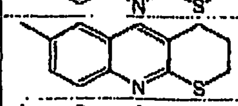
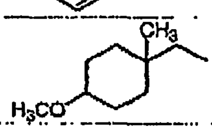
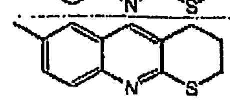
Table 7

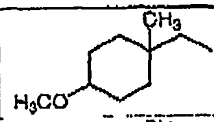
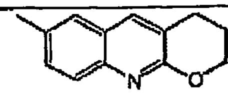
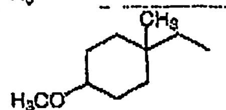
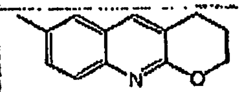
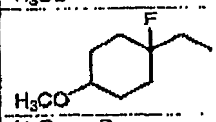
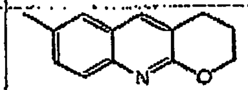
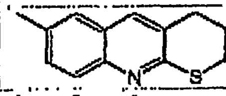
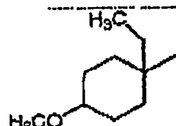
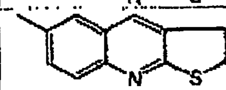
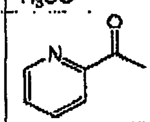
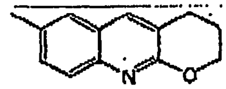
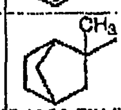
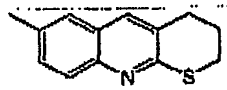
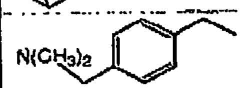
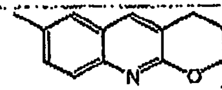
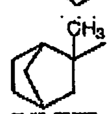
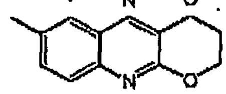
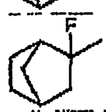
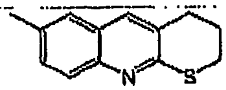
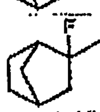
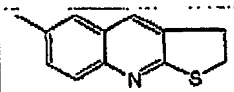
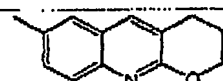
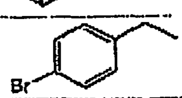
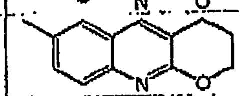
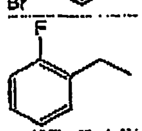
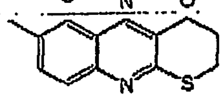


Co. no.	Ex. no.	R^1	L	physical data
432	B16			mp.:128°C
433	B4			mp.:175°C
434	B4			mp.:170°C
435	B4			mp.:103°C
436	B4			mp.:151°C
437	B4			(trans); mp.:110°C
438	B4			mp.:150°C
439	B4			mp.:150°C
440	B4			(cis)

Co. no.	Ex. no.	R^1	L	physical data
441	B4			mp.:166°C
442	B4			mp.:173°C
443	B4			mp.:208°C
444	B4			mp.:149°C
445	B4			mp.:133°C
446	B3b			mp.:150°C
447	B3b			mp.:165°C
448	B3b			mp.:147°C
449	B3b			mp.:154°C
450	B3b			mp.:157°C
451	B4			mp.:190°C
452	B4			mp.:187°C
453	B3b			mp.:200°C
454	B3b			mp.:160°C

Co. no.	Ex. no.	R^1	L	physical data
455	B3b			mp.:139°C
456	B3b			(A); mp.:174°C
457	B3b			(B); mp.:160°C
458	B3b			mp.:184°C
459	B4			-
460	B4			mp.:134°C
461	B4			(B); mp.:156°C
462	B4			mp.:153°C
463	B3b			mp.:161°C
464	B4			mp.:135°C
465	B4			mp.:131°C
466	B3b			.HCl(1:1); mp.:206°C
467	B3d			mp.:142°C
468	B4			.hydrate(1:1); mp.:104°C
469	B3b	dimethylethyl		mp.:104°C

Co. no.	Ex. no.	R^1	L	physical data
470	B3b			mp.:161°C
472	B3b			mp.:144°C
473	B4			mp.:143°C
474	B4			mp.:196°C
475	B4			mp.:162°C
476	B4			mp.:171°C
477	B4			mp.:155°C
478	B2	trimethylmethyl		mp.:124°C
479	B4			(A); mp.:146°C
480	B4			(B); mp.:162°C
481	B4			(A); mp.:129°C
482	B4			mp.:115°C
483	B2			mp.:187°C
484	B2			mp.:162°C
485	B4			(A); mp.:130°C

Co. no.	Ex. no.	R[1]	L	physical data
486	B4			(A); mp.:124°C
487	B4			(B); mp.:128°C
488	B4			mp.:85°C
489	B2			mp.:150°C
490	B4			(A); mp.:117°C
491	B2			mp.:220°C
492	B4			mp.:136°C
493	B2			mp.:131°C
494	B4			(A); mp.:125°C
495	B4			mp.:135°C
496	B4			mp.:139°C
497	B4			mp.:127°C
498	B16			mp.:195°C
499	B2			mp.:201°C

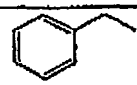
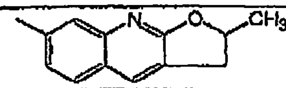
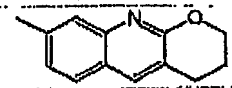
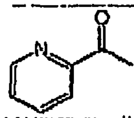
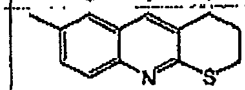
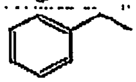
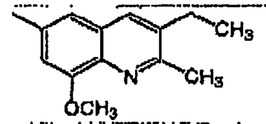
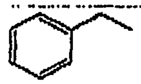
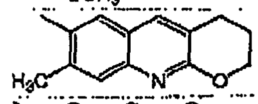
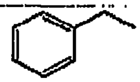
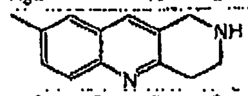
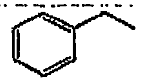
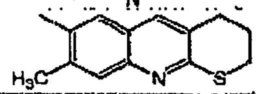
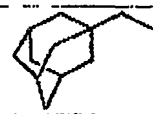
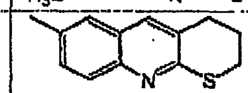
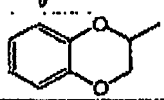
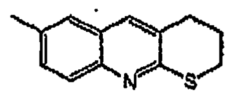
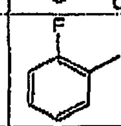
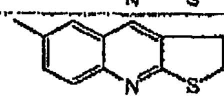
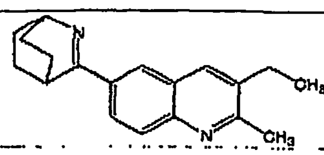
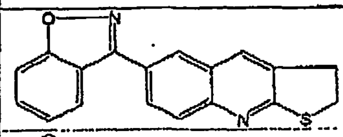
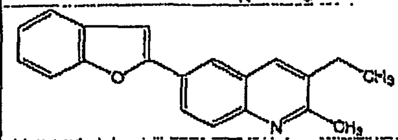
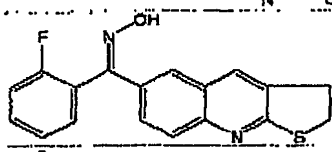
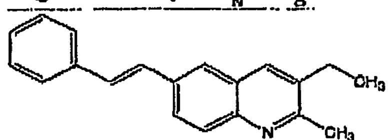
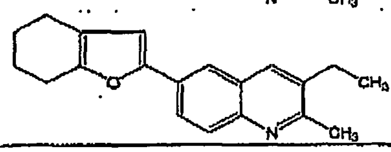
Co. no.	Ex. no.	R^1	L	physical data
500	B3b			mp.:143°C
501	B3b			mp.:137°C
502	B2			mp.:210°C
503	B3d			mp.:134°C
504	B2			mp.:163°C
505	B4			mp.:142°C
506	B2			mp.:139°C
507	B4			mp.:171°C
512	B3b			-
523	B3b			-

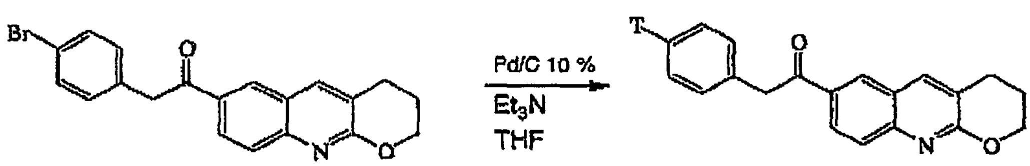
Table 8:

Co. no.	Ex. no.	Structure	physical data
511	B11		-

Co. no.	Ex. no.	Structure	physical data
514	B12		-
515	B13		-
524	B9a		mp.:185°C
471	B15		(E)
526	B14		.HCl(1:1)

C. Preparation of radioactively labelled compounds

C.1 [^{3}H]-labelled compounds



Compound 498 Compound 528

To a carefully measured amount of palladium on carbon (10 %, 0.872 mg) was added a solution of compound 498 (I, 0.919 mg, 2.4 μmol) and triethylamine (0.92 μl, 6.6 μmol) in sodium-dried tetrahydrofuran (175 μl). The reaction flask was connected to a tritiation manifold system and the reaction mixture was carefully degassed. Tritium gas (19.5 Ci at a pressure of 1017 mbar) was generated from uranium tritide and was

allowed onto the at room temperature stirred reaction mixture. After 30 min, the reaction mixture was frozen with liquid nitrogen and the excess of tritium gas was recaptured onto uranium sponge. The solvent was lyophilized from the reaction mixture. Methanol (100 μl) was introduced and lyophilized in order to remove labile tritium. This procedure was repeated twice more. The residue was taken up in ethanol, filtered over a GHP Acrodisk 13 mm syringe filter and depleted with ethanol to a total volume of 50.0 ml. It contained 71 mCi of radioactivity with [^{3}H]-compound 528 (II) at a 67 % radiochemical purity. From this amount, a fraction (5.0 ml) was taken and thoroughly purified in portions via preparative HPLC (Kromasil KR 100-10, column dimensions 4.6 mm ID x 300 mm). UV detection took place at 265 nm. Elution was performed isocratically with water-methanol-acetonitrile-diisopropylamine (47:26.5:26.5:0.2; v/v/v/v) at a flow rate of 2.0 ml/min. The product containing fractions were combined and concentrated under vacuum at 30°C. The residue was dissolved in ethanol (5.0 ml) and concentrated again. This procedure was repeated twice more. The remaining residue was finally dissolved in ethanol (20.0 ml) and stored as such. The batch contained [^{3}H]-compound 528 (II) with a total radioactivity of 3.83 mCi at a purity > 98 % and at a specific activity of about 25 Ci/mmol.

D. Pharmacological examples

D1. Signal transduction at the cloned rat mGluR1 receptor in CHO cells

CHO cells expressing the mGluR1 receptor were plated in precoated black 96-well plates. The next day, the effect of the present compounds on glutamate-activated intracellular Ca^{2+} increase was evaluated in a fluorescent based assay. The cells were loaded with Fluo-3 AM, plates were incubated for 1 hour at room temperature in the dark, cells were washed and the present compounds were added onto the cells for 20 minutes. After this incubation time, the glutamate-induced Ca^{2+} rise was recorded for each well in function of time using the Fluorescent Image Plate Reader (FLIPR, Molecular Devices Inc.). Relative fluorescence units were recorded and average data graphs of quadruple wells were obtained. Concentration-response curves were constructed based on peak fluorescence (maximum signal between 1 and 90 secondes) for each concentration of tested compound. pIC_{50} values are the –log values of the concentration of the tested compounds resulting in 50% inhibition of the glutamate-induced intracellular Ca^{2+} rise.

The compounds according to the present invention exhibited a pIC_{50} value of at least 5.

The compounds that are included in the Tables 1-8 exhibited a pIC_{50} value of at least 6.

A particular group of compounds exhibited a pIC_{50} value between 7 and 8. It concerns the compounds listed in Table 9.

Table 9:

Com.nr.	pIC_{50}
463	7.98
441	7.95
334	7.95
22	7.94
421	7.94
15	7.93
440	7.93
139	7.93
178	7.92
338	7.91
87	7.90
462	7.90
394	7.90
423	7.89
21	7.87
220	7.87
479	7.86
483	7.86
485	7.84
9	7.84
110	7.84
248	7.84
341	7.83
163	7.81
433	7.79
238	7.79
224	7.78
437	7.78
498	7.78
449	7.77

Com.nr.	pIC_{50}
281	7.63
487	7.63
299	7.63
431	7.61
98	7.57
464	7.57
446	7.56
251	7.55
484	7.54
494	7.53
128	7.52
344	7.52
161	7.49
298	7.48
454	7.45
456	7.45
277	7.44
91	7.43
356	7.42
229	7.41
333	7.41
326	7.41
369	7.40
430	7.39
435	7.38
35	7.36
228	7.36
429	7.36
117	7.35
291	7.35

Com.nr.	pIC_{50}
89	7.25
108	7.25
373	7.25
255	7.23
527	7.23
303	7.22
296	7.22
221	7.21
193	7.21
14	7.20
131	7.19
438	7.19
148	7.18
496	7.18
236	7.17
332	7.17
481	7.16
191	7.16
457	7.14
20	7.14
145	7.13
268	7.13
512	7.13
474	7.13
10	7.11
307	7.11
426	7.11
466	7.10
97	7.08
83	7.08

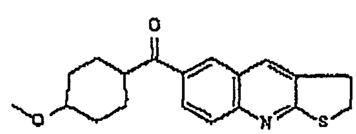
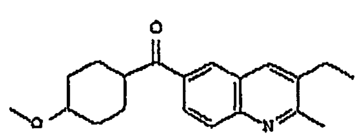
Com.nr.	pIC_{50}
242	7.76
346	7.74
182	7.73
486	7.73
447	7.72
7	7.72
175	7.71
475	7.71
480	7.71
213	7.70
239	7.70
241	7.67
461	7.65
115	7.64
445	7.63

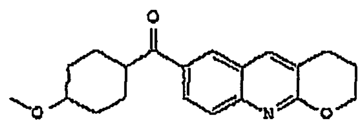
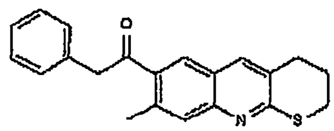
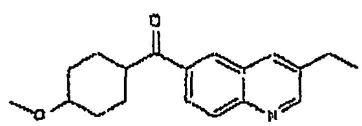
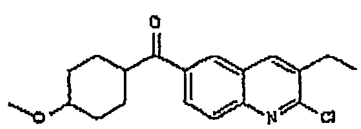
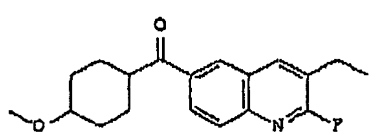
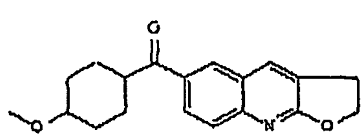
Com.nr.	pIC_{50}
313	7.35
280	7.34
460	7.34
482	7.34
343	7.33
425	7.32
473	7.32
287	7.31
448	7.31
243	7.29
323	7.28
159	7.28
289	7.27
184	7.26
436	7.26

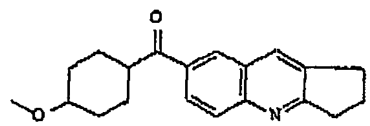
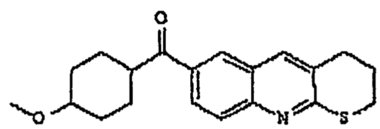
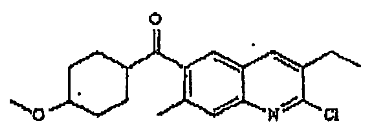
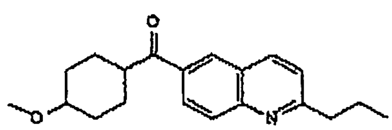
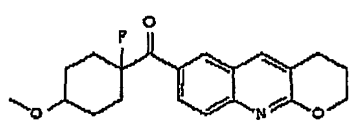
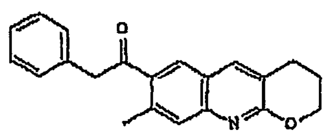
Com.nr.	pIC_{50}
434	7.08
300	7.08
199	7.07
290	7.06
112	7.05
348	7.05
286	7.03
442	7.03
422	7.02
283	7.02
318	7.02
36	7.00
396	7.00

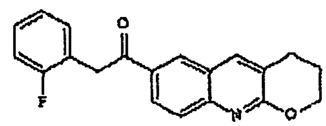
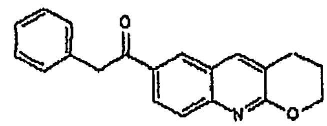
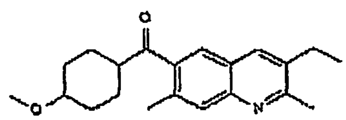
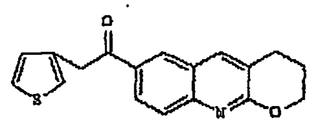
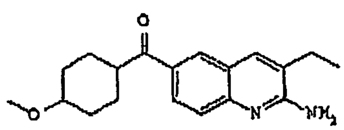
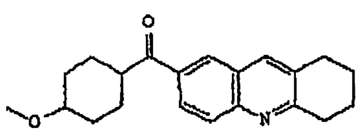
A particular group of compounds exhibited a pIC_{50} value of at least 8. It concern the compounds listed in Table 10.

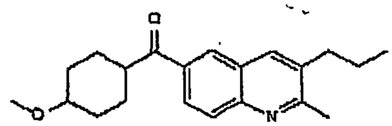
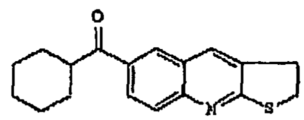
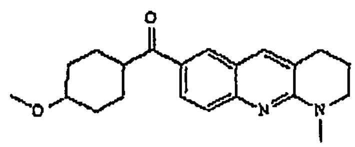
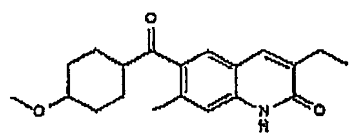
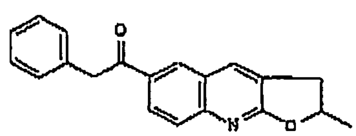
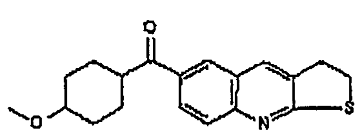
Table 10 :

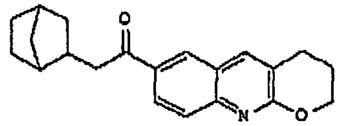
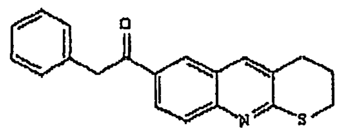
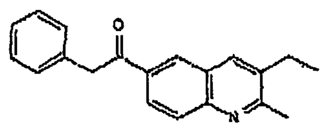
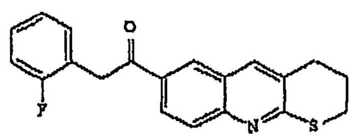
Comp. nr.	Structure	pIC50
416	 (CIS)	8.587
27	 (CIS)	8.527

Comp. nr.	Structure	pIC50
174	 (CIS)	8.49
506		8.48
25	 (CIS)	8.45
4	 (CIS)	8.4
19	 (CIS)	8.38
429	 (CIS)	8.38

Comp. nr.	Structure	pIC50
424	 (CIS)	8.355
176	 (CIS)	8.33
210	 (CIS)	8.315
114	 (CIS)	8.28
488		8.27
504		8.27

Comp. nr.	Structure	pIC50
477		8.25
432		8.237
214	 (CIS)	8.233
465		8.145
135	 (CIS)	8.14
420	 (CIS) Hydrochloride (1:1)	8.135

Comp. nr.	Structure	pIC50
292	 (CIS)	8.13
427		8.115
208	 (CIS)	8.095
419	 (CIS)	8.065
455		8.055
418	 (TRANS)	8.045

Comp. nr.	Structure	pIC50
497		8.025
439		8.023
237		8.01
499		8

D2. *In vitro* binding experiments with a [^{3}H]-radiolabelled compound according to the invention

As [^{3}H]-radiolabelled compound is used : compound 528, hereafter named as [^{3}H]Compound A, which is the radiolabelled equivalent of compound 432.

Cell membrane fractions, prepared from either CHO-cells transfected with the rat mGlu1a receptor and L929sA-cells transfected with the human mGlu1a receptor according to Mutel et al., J. Neurochem. 75, 2590-2601, 2000 - were incubated for 1 hour at room temperature in 6 different membrane protein concentrations (0, 20, 50, 80, 100, 150 µg protein/assay) with a radioactive [^{3}H]-labelled substance (described hereinafter as the [^{3}H]-ligand). This [^{3}H]-ligand is known to bind specifically to the mGlu1 receptor, thus labeling this receptor. The [^{3}H]-ligand used is mentioned in Table 11. After the incubation, the labelled membranes were harvested on GF/C glass fibre filters and rinsed three times with 3 ml of a cold buffer solution to remove non-bound [^{3}H]-ligands. Subsequently the glass fibre filters, with the harvested membranes, were placed in plastic mini-vials and 3.0 ml of Ultima Gold™ scintillation cocktail was added. After overnight incubation, the vials were vigorously shaken and the radioactivity was counted in a Packard Tri-Carb 1500 CA liquid scintillation analyzer. Said radioactivity is proportional to the membrane labelling by the [^{3}H]-ligand. Specific membrane labelling by the [^{3}H]-ligand was distinguished from the non-specific membrane labelling by selectively inhibiting the labelling of the receptor site by another substance (unlabelled) known to compete with the [^{3}H]-ligand for binding to said receptor site. As competing substance, compound 135 was used for the [^{3}H]Compound A ligand and glutamate for the [^{3}H]-Quisqualate ligand. The non-specific binding is expressed as the ratio of the total binding over the binding in the presence of the competing substance in percentage and should be as small as possible.

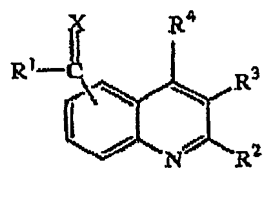
From Table 11, it can be seen that the non-specific binding is excellent for the compound according to the invention.

Table 11 : Non Specific Binding (NSB) for different mGluR1 ligands for different concentrations.

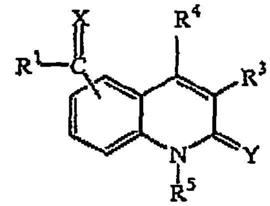
µg/assay	20	50	80	100	150
rat-mGlu1a receptor					
[^{3}H]-Quisqualate	39	18	9	11	9
[^{3}H]Compound A	7	3	3	3	2
human-mGlu1a receptor					
[^{3}H]-Quisqualate	75	40	43	49	34
[^{3}H]Compound A	72	53	46	46	38

CLAIMS

1. A radiolabelled compound according to Formula (I-A)* or (I-B)*



(I-A)*



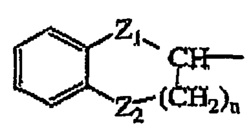
(I-B)*

an *N*-oxide form, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof, wherein

X represents O; $C(R^6)_2$ with R^6 being hydrogen, aryl or C_{1-6}alkyl optionally substituted with amino or mono- or di(C_{1-6}alkyl)amino; S or N-R^7 with R^7 being amino or hydroxy;

R^1 represents C_{1-6}alkyl; aryl; thienyl; quinolinyl; cycloC_{3-12}alkyl or (cycloC_{3-12}alkyl)C_{1-6}alkyl, wherein the cycloC_{3-12}alkyl moiety optionally may contain a double bond and wherein one carbon atom in the cycloC_{3-12}alkyl moiety may be replaced by an oxygen atom or an NR^8-moiety with R^8 being hydrogen, benzyl or C_{1-6}alkyloxycarbonyl ; wherein one or more hydrogen atoms in a C_{1-6}alkyl-moiety or in a cycloC_{3-12}alkyl-moiety optionally may be replaced by C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, aminoC_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, halo, C_{1-6}alkyloxycarbonyl, aryl, amino, mono– or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, halo, piperazinyl, pyridinyl, morpholinyl, thienyl or a bivalent radical of formula –O–, -O-CH_2-O or –O-CH_2-CH_2-O-;

or a radical of formula (a-1)



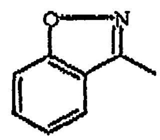
a-1

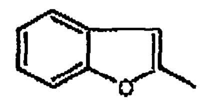
wherein Z_1 is a single covalent bond, O, NH or CH_2;
Z_2 is a single covalent bond, O, NH or CH_2;
n is an integer of 0, 1, 2 or 3;

and wherein each hydrogen atom in the phenyl ring independently may optionally be replaced by halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy or hydroxyC_{1-6}alkyl;

or X and R^1 may be taken together with the carbon atom to which X and R^1 are attached to form a radical of formula (b-1), (b-2) or (b-3);


b-1


b-2


b-3

R^2 represents hydrogen; halo; cyano; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkylthio; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylcarbonyloxyC_{1-6}alkyl; C_{2-6}alkenyl; hydroxyC_{2-6}alkenyl; C_{2-6}alkynyl; hydroxyC_{2-6}alkynyl; tri(C_{1-6}alkyl)silaneC_{2-6}alkynyl; amino; mono– or di(C_{1-6}alkyl)amino; mono– or di(C_{1-6}alkyloxyC_{1-6}alkyl)amino; mono– or di(C_{1-6}alkylthioC_{1-6}alkyl)amino; aryl; arylC_{1-6}alkyl; arylC_{2-6}alkynyl; C_{1-6}alkyloxyC_{1-6}alkylaminoC_{1-6}alkyl; aminocarbonyl optionally substituted with C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl or pyridinylC_{1-6}alkyl;
a heterocycle selected from thienyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, piperidinyl and piperazinyl, optionally N-substituted with C_{1-6}alkyloxyC_{1-6}alkyl, morpholinyl, thiomorpholinyl, dioxanyl or dithianyl ;
a radical –NH-C(=O)R^9 wherein R^9 represents
C_{1-6}alkyl optionally substituted with cycloC_{3-12}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aryl, aryloxy, thienyl, pyridinyl, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylthio, benzylthio, pyridinylthio or pyrimidinylthio;
cycloC_{3-12}alkyl; cyclohexenyl; amino; arylcycloC_{3-12}alkylamino; mono-or-di(C_{1-6}alkyl)amino; mono- or di(C_{1-6}alkyloxycarbonylC_{1-6}alkyl)amino; mono- or di(C_{1-6}alkyloxycarbonyl)amino; mono-or di(C_{2-6}alkenyl)amino; mono- or di(arylC_{1-6}alkyl)amino; mono- or diarylamino; arylC_{2-6}alkenyl; furanylC_{2-6}alkenyl; piperididinyl; piperazinyl; indolyl; furyl; benzofuryl; tetrahydrofuryl; indenyl; adamantyl; pyridinyl; pyrazinyl; aryl; arylC_{1-6}alkylthio or a radical of formula (a-1) ;

a sulfonamid -NH-SO_2-R^{10} wherein R^{10} represents C_{1-6}alkyl, mono- or poly haloC_{1-6}alkyl, arylC_{1-6}alkyl, arylC_{2-6}alkenyl, aryl, quinolinyl, isoxazolyl or di(C_{1-6}alkyl)amino;

R^3 and R^4 each independently represent hydrogen; halo; hydroxy; cyano; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyloxyC_{1-6}alkyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{2-6}alkenyl; hydroxyC_{2-6}alkenyl; C_{2-6}alkynyl; hydroxyC_{2-6}alkynyl; tri(C_{1-6}alkyl)silaneC_{2-6}alkynyl; amino; mono– or di(C_{1-6}alkyl)amino; mono– or di(C_{1-6}alkyloxyC_{1-6}alkyl)amino; mono– or di(C_{1-6}alkylthioC_{1-6}alkyl)amino; aryl; morpholinylC_{1-6}alkyl or piperidinylC_{1-6}alkyl ; or

R^2 and R^3 may be taken together to form $-R^2-R^3-$, which represents a bivalent radical of formula $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, -CH=CH-CH=CH-, $-Z_4$-CH=CH-, -CH=CH-Z_4-, $-Z_4$-CH_2-CH_2-CH_2-, -CH_2-Z_4-CH_2-CH_2-, -CH_2-CH_2-Z_4-CH_2-, -CH_2-CH_2-CH_2-Z_4-, -Z_4-CH_2-CH_2-, -CH_2-Z_4-CH_2- or -CH_2-CH_2-Z_4-, with Z_4 being O, S, SO_2 or NR^{11} wherein R^{11} is hydrogen, C_{1-6}alkyl, benzyl or C_{1-6}alkyloxycarbonyl; and wherein each bivalent radical is optionally substituted with C_{1-6}alkyl.

or R^3 and R^4 may be taken together to form a bivalent radical of formula -CH=CH-CH=CH- or -CH_2-CH_2-CH_2-CH_2- ;

R^5 represents hydrogen; cycloC_{3-12}alkyl; piperidinyl; oxo-thienyl; tetrahydrothienyl, arylC_{1-6}alkyl; C_{1-6}alkyloxyC_{1-6}alkyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl or C_{1-6}alkyl optionally substituted with a radical C(=O)NR_xR_y, in which R_x and R_y, each independently are hydrogen, cycloC_{3-12}alkyl, C_{2-6}alkynyl or C_{1-6}alkyl optionally substituted with cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, furanyl, pyrrolidinyl, benzylthio, pyridinyl, pyrrolyl or thienyl;

Y represents O or S;

or Y and R^5 may be taken together to form =Y-R^5- which represents a radical of formula

-CH=N-N= (c-1);

-N=N-N= (c-2); or

-N-CH=CH- (c-3);

aryl represents phenyl or naphthyl optionally substituted with one or more substituents selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, phenyloxy, nitro, amino, thio, C_{1-6}alkylthio, haloC_{1-6}alkyl, polyhaloC_{1-6}alkyl, polyhaloC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, aminoC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino; mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyano, -CO-R^{12}, -CO-OR^{13},

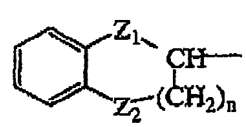
$-NR^{13}SO_2R^{12}$, $-SO_2-NR^{13}R^{14}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{13}R^{14}$, $-SOR^{12}$, $-SO_2R^{12}$; wherein each R^{12}, R^{13} and R^{14} independently represent C_{1-6}alkyl; cycloC_{3-6}alkyl; phenyl; phenyl substituted with halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, haloC_{1-6}alkyl, polyhaloC_{1-6}alkyl, furanyl, thienyl, pyrrolyl, imidazolyl, thiazolyl or oxazolyl;

and when the R^1-C(=X) moiety is linked to another position than the 7 or 8 position, then said 7 and 8 position may be substituted with R^{15} and R^{16} wherein either one or both of R^{15} and R^{16} represents C_{1-6}alkyl, C_{1-6}alkyloxy or R^{15} and R^{16} taken together may form a bivalent radical of formula -CH=CH-CH=CH-.

2. A radiolabelled compound according to claim 1, characterized in that,

X represents O; $C(R^6)_2$ with R^6 being hydrogen or aryl ; or N-R^7 with R^7 being amino or hydroxy;

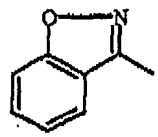
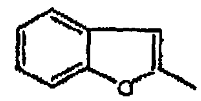
R^1 represents C_{1-6}alkyl, aryl; thienyl; quinolinyl; cycloC_{3-12}alkyl or (cycloC_{3-12}alkyl)C_{1-6}alkyl, wherein the cycloC_{3-12}alkyl moiety optionally may contain a double bond and wherein one carbon atom in the cycloC_{3-12}alkyl moiety may be replaced by an oxygen atom or an NR^8-moiety with R^8 being benzyl or C_{1-6}alkyloxycarbonyl ; wherein one or more hydrogen atoms in a C_{1-6}alkyl-moiety or in a cycloC_{3-12}alkyl-moiety optionally may be replaced by C_{1-6}alkyl, haloC_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, halo, aryl, mono– or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, halo, piperazinyl, pyridinyl, morpholinyl, thienyl or a bivalent radical of formula –O- or -O-CH_2-CH_2-O-; or a radical of formula (a-1)



a-1

wherein Z_1 is a single covalent bond, O or CH_2;
Z_2 is a single covalent bond, O or CH_2;
n is an integer of 0, 1, or 2 ;
and wherein each hydrogen atom in the phenyl ring independently may optionally be replaced by halo or hydroxy;

or X and R^1 may be taken together with the carbon atom to which X and R^1 are attached to form a radical of formula (b-1), (b-2) or (b-3);

b-1 b-2 b-3

R^2 represents hydrogen; halo; cyano; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkylthio; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{2-6}alkenyl; hydroxyC_{2-6}alkenyl; C_{2-6}alkynyl; hydroxyC_{2-6}alkynyl; tri(C_{1-6}alkyl)silaneC_{2-6}alkynyl; amino; mono– or di(C_{1-6}alkyl)amino; mono– or di(C_{1-6}alkyloxyC_{1-6}alkyl)amino; mono– or di(C_{1-6}alkylthioC_{1-6}alkyl)amino; aryl; arylC_{1-6}alkyl; arylC_{2-6}alkynyl; C_{1-6}alkyloxyC_{1-6}alkylaminoC_{1-6}alkyl;
aminocarbonyl optionally substituted with C_{1-6}alkyloxycarbonylC_{1-6}alkyl ;
a heterocycle selected from thienyl, furanyl, thiazolyl and piperidinyl, optionally N-substituted with morpholinyl or thiomorpholinyl;
a radical –NH-C(=O)R^9 wherein R^9 represents C_{1-6}alkyl optionally substituted with cycloC_{3-12}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, aryl, aryloxy, thienyl, pyridinyl, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkylthio, benzylthio, pyridinylthio or pyrimidinylthio; cycloC_{3-12}alkyl; cyclohexenyl; amino; arylcycloC_{3-12}alkylamino; mono-or-di(C_{1-6}alkyl)amino; mono- or di(C_{1-6}alkyloxycarbonylC_{1-6}alkyl)amino; mono- or di(C_{1-6}alkyloxycarbonyl)amino; mono-or di(C_{2-6}alkenyl)amino; mono- or di(arylC_{1-6}alkyl)amino; mono- or diarylamino; arylC_{2-6}alkenyl; furanylC_{2-6}alkenyl; piperididinyl; piperazinyl; indolyl; furyl; benzofuryl; tetrahydrofuryl; indenyl; adamantyl; pyridinyl; pyrazinyl; aryl or a radical of formula (a-1) ;
a sulfonamid -NH-SO_2-R^{10} wherein R^{10} represents C_{1-6}alkyl, mono- or poly haloC_{1-6}alkyl, arylC_{1-6}alkyl or aryl;

R^3 and R^4 each independently represent hydrogen; C_{1-6}alkyl; C_{1-6}alkyloxyC_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; or

R^2 and R^3 may be taken together to form $-R^2$-R^3-, which represents a bivalent radical of formula $-(CH_2)_4$-, $-(CH_2)_5$-, $-Z_4$-CH=CH-, $-Z_4$-CH_2-CH_2-CH_2- or $-Z_4$-CH_2-CH_2-, with Z_4 being O, S, SO_2 or NR^{11} wherein R^{11} is hydrogen, C_{1-6}alkyl, benzyl or C_{1-6}alkyloxycarbonyl; and wherein each bivalent radical is optionally substituted with C_{1-6}alkyl;

or R^3 and R^4 may be taken together to form a bivalent radical of formula -CH=CH-CH=CH- or $-CH_2$-CH_2-CH_2-CH_2- ;

R^5 represents hydrogen; piperidinyl; oxo-thienyl; tetrahydrothienyl, arylC_{1-6}alkyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl or C_{1-6}alkyl optionally substituted with a radical

$C(=O)NR_xR_y$, in which R_x and R_y, each independently are hydrogen, cycloC_{3-12}alkyl, C_{2-6}alkynyl or C_{1-6}alkyl optionally substituted with cyano, C_{1-6}alkyloxy or C_{1-6}alkyloxycarbonyl;

Y represents O or S;

or Y and R^5 may be taken together to form $=Y-R^5-$ which represents a radical of formula

-CH=N-N= (c-1); or

-N=N-N= (c-2);

aryl represents phenyl or naphthyl optionally substituted with one or more substituents selected from halo, C_{1-6}alkyloxy, phenyloxy, mono-or di(C_{1-6}alkyl)amino and cyano;

and when the R^1-C(=X) moiety is linked to another position than the 7 or 8 position, then said 7 and 8 position may be substituted with R^{15} and R^{16} wherein either one or both of R^{15} and R^{16} represents C_{1-6}alkyl or R^{15} and R^{16} taken together may form a bivalent radical of formula -CH=CH-CH=CH-.

3. A radiolabelled compound according to any one of claims 1 - 2, characterized in that,

X represents O;

R^1 represents C_{1-6}alkyl; cycloC_{3-12}alkyl or (cycloC_{3-12}alkyl)C_{1-6}alkyl, wherein one or more hydrogen atoms in a C_{1-6}alkyl-moiety or in a cycloC_{3-12}alkyl-moiety optionally may be replaced by C_{1-6}alkyloxy, aryl, halo or thienyl;

R^2 represents hydrogen; halo; C_{1-6}alkyl or amino;

R^3 and R^4 each independently represent hydrogen or C_{1-6}alkyl; or

R^2 and R^3 may be taken together to form $-R^2-R^3-$, which represents a bivalent radical of formula $-Z_4-CH_2-CH_2-CH_2-$ or $-Z_4-CH_2-CH_2-$ with Z_4 being O or NR^{11} wherein R^{11} is C_{1-6}alkyl; and wherein each bivalent radical is optionally substituted with C_{1-6}alkyl;

or R^3 and R^4 may be taken together to form a bivalent radical of formula $-CH_2-CH_2-CH_2-CH_2-$;

R^5 represents hydrogen;

Y represents O; and

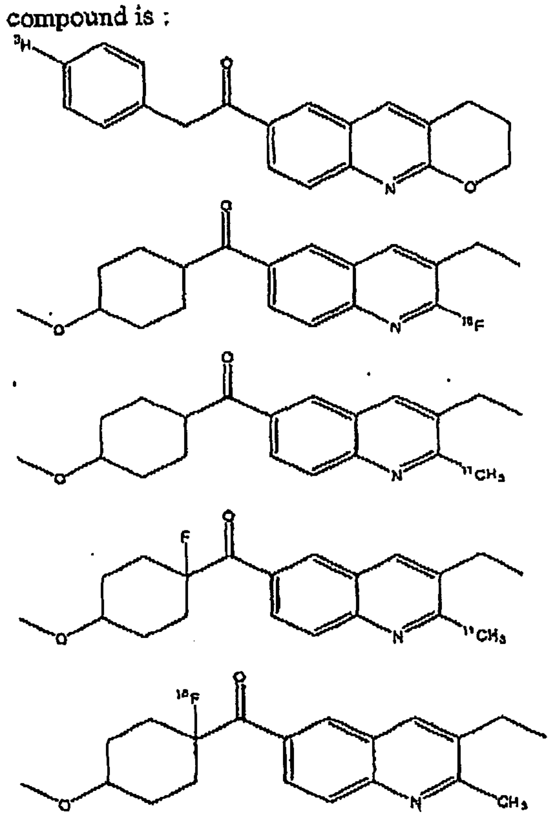
aryl represents phenyl optionally substituted with halo.

4. A radiolabelled compound according to any one of claims 1-3, characterized in that the R^1-C(=X) moiety is linked to the quinoline or quinolinone moiety in position 6.

5. A radiolabelled compound according to any one of claims 1 - 4, characterized in that the compound contains at least one radioactive atom.

6. A radiolabelled compound according to claim 5, characterized in that the radioactive isotope is selected from the group of of ^{3}H, ^{11}C and ^{18}F.

7. A radiolabelled compound according to claim 6, characterized in that the compound is :



8. Radioactive composition for the administration to mamals comprising a therapeutically effective amount of a radiolabelled compound of Formula (I-A)* or (I-B)* and a pharmaceutically acceptable carrier or diluent.

9. A radiolabelled compound or composition according to any one of claims 1-8 for use in a diagnostic method.

10. A radiolabelled compound or composition according to claim 9, characterized in that the diagnostic method consists of marking or identifying a mGlu1 receptor in biological material.

11. A radiolabelled compound or composition according to claim 10, characterized in that the marking consists of administering the radiolabelled compound to biological material and the identifying consists of detecting the emissions from the radiolabelled compound.

12. A radiolabelled compound or composition according to claim 9, characterized in that the diagnostic method consists of screening whether a test compound has the ability to occupy or bind to a mGlu1 receptor in biological material.

13. A radiolabelled compound or composition according to any one of claims 10 - 12, characterized in that the biological material is selected from the group of tissue samples, plasma fluids, body fluids, body parts and organs originating from warm-blooded animals and warm-blooded animals *per se*, in particular humans.

14. Use of a radiolabelled compound or composition according to any one of claims 1 - 8 for the manufacture of a diagnostic tool for marking or identifying an mGlu1 receptor in biological material.

15. Use of a radiolabelled compound or composition according to claim 14, characterized in that the marking consists of administering the radiolabelled compound to biological material and the identifying consists of detecting the emissions from the radiolabelled compound.

16. Use of a radiolabelled compound or composition according to any one of claims 1-8 for the manufacture of a diagnostic tool for screening whether a test compound has the ability to occupy or bind to a mGlu1 receptor in biological material

17. Use of a radiolabelled compound or composition according to any of claims 1- 8 for the manufacture of a diagnostic tool for imaging an organ, characterized by administering a sufficient amount of a radiolabelled compound or composition according to any one of claims 1-8 in an appropriate composition to biological material, whereby said radiolabelled compound binds to a mGlu1 receptor sites in

the biological material ; and detecting the emissions from the radiolabelled compound.

18. Use of a radiolabelled compound or composition according to claim 17 for the manufacture of a diagnostic tool for imaging an organ, characterized in that the imaging is performed using Positron Emission Tomography (PET).

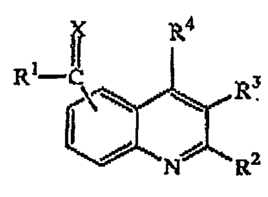
19. Use of a radiolabelled compound or composition according to any one of claims 14 to 18, characterized in that the biological material is selected from the group of tissue samples, plasma fluids, body fluids, body parts and organs originating from warm-blooded animals and warm-blooded animals *per se*, in particular humans.

JAB 1703

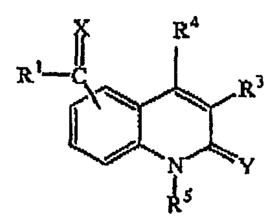
ABSTRACT

RADIOLABELLED QUINOLINE AND QUINOLINONE DERIVATIVES AND THEIR USE AS METABOTROPIC GLUTAMATE RECEPTOR LIGANDS.

The present invention is concerned with radiolabelled quinoline and quinolinone derivatives according Formula (I-A)* or (I-B)* showing metabotropic glutamate receptor antagonistic activity, in particular mGlu1 receptor activity, and their preparation ; it further relates to compositions comprising them, as well as their use for marking and identifying metabotropic glutamate receptor sites and for imaging an organ.



(I-A)*



(I-B)*

In a preferable embodiment, X represents O; R^1represents C_{1-6}alkyl; cycloC_{3-12}alkyl or (cycloC_{3-12}alkyl)C_{1-6}alkyl, wherein one or more hydrogen atoms in a C_{1-6}alkyl-moiety or in a cycloC_{3-12}alkyl-moiety optionally may be replaced by C_{1-6}alkyloxy, aryl, halo or thienyl; R^2 represents hydrogen; halo; C_{1-6}alkyl or amino; R^3 and R^4 each independently represent hydrogen or C_{1-6}alkyl; or R^2 and R^3 may be taken together to form $-R^2-R^3-$, which represents a bivalent radical of formula $-Z_4-CH_2-CH_2-CH_2-$ or $-Z_4-CH_2-CH_2-$ with Z_4 being O or NR^{11} wherein R^{11} is C_{1-6}alkyl; and wherein each bivalent radical is optionally substituted with C_{1-6}alkyl; or R^3 and R^4 may be taken together to form a bivalent radical of formula $-CH_2-CH_2-CH_2-CH_2-$; R^5 represents hydrogen; Y represents O; and aryl represents phenyl optionally substituted with halo. Most preferred are radiolabelled compounds in which the radioactive isotope is selected from the group of of ^3H, ^{11}C and ^{18}F. The invention also relates to their use in a diagnostic method, in perticular for marking and identifying a mGluR1 receptor in biological material, as well as to their use for imaging an organ, in particular using PET.